Chapter 6

Respiratory Health Effects

6.0 Introduction

The relationship between ETS exposure and a variety of nonmalignant respiratory tract health endpoints has been examined extensively in the epidemiologic and experimental literature. Among children, the most common outcomes studied include asthma induction and exacerbation, alterations in lung development, and otitis media and chronic middle ear effusions in children. Among adults, endpoints of interest have included lower respiratory tract symptoms, lung function, and acute irritative symptoms of the upper respiratory tract. Each of the lower respiratory tract endpoints, as well as otitis media, were reviewed in reports by the Surgeon General's Office (U.S. DHHS, 1986), the National Research Council (NRC, 1986), and most recently by the U.S. Environmental Protection Agency (U.S. EPA, 1992); upper respiratory tract irritation and sensory annoyance were reviewed in the Surgeon General's and NRC reports only. This chapter synthesizes the data considered in these prior literature reviews with results from more recent studies in order to assess the possible relationship between ETS exposure and each of the above-mentioned health endpoints.

6.1 Acute Health Effects

6.1.1 Asthma (exacerbation)

Asthma is a chronic respiratory condition characterized by airway inflammation and episodic airflow limitation. Depending on the clinical definition used, about 2-3% of adults and up to 10% of children may be affected (Evans *et al.*, 1987; Schwartz *et al.*, 1990; Gergen *et al.*, 1990; Gerstman *et al.*, 1989). Asthma is the most common chronic condition of childhood, and in 1990 accounted for approximately $6.2 billion in health care expenditures nationally (CDC, 1992). No similar cost estimate is available for California; however, in the state in 1993 there were approximately 43,000 admissions to hospital with a primary diagnosis of asthma, about 18,600 of which were for children under age 18 (Personal communication: Dr. Marvin Bohnstedt, California Department of Health Services). Typical symptoms of asthma include cough, chest tightness, difficulty breathing, and wheezing. One of the hallmarks of asthma is airway hyperresponsiveness, an exaggerated tendency of the airways to constrict in response to physical stimuli, such as cold, dry air, or chemical agents, such as methacholine or histamine.

In its recent review, the U.S. EPA (1992) concluded that, “There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease” (p. 248). This conclusion appears to have been based on a review of several studies summarized in Table 6.1. These and additional relevant studies are described in the following pages.

TABLE 6.1: STUDIES CITED BY U.S. EPA (1993) AS EVIDENCE SUPPORTING A CAUSAL RELATION BETWEEN ETS EXPOSURE AND INCREASED EPISODES AND SEVERITY OF ASTHMA IN CHILDREN

Authors	Population Studied	ETS Exposure Assessment	Outcome Variable	Results[1]	Observations
Evans *et al.* (1987)	191 children aged 4 to 17 yr. in New York, New York	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1± 0.4 vs. 1.8 ± 0.3* (p=0.008) emergency room visits per year in children of smoking and nonsmoking parents *mean ± standard error	No distinction made between maternal and paternal smoking; independent of race and parental employment status
O'Connor *et al.* (1987)	292 subjects aged 6 to 21 yr. in Boston, Massachusetts	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatic subjects whose mothers smoked	No increase in non-asthmatic subjects whose mothers smoked
Murray and Morrison (1989)	415 children aged 1 to 17 yr with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p<0.01$) in children of smoking mothers	Stronger effect in boys and older children
Oldigs *et al.* (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assessment of effect of chronic exposure
Ehrlich *et al.* (1992)	228 children: 72 with acute asthma, 35 with nonacute asthma, and 121 controls	Cotinine levels in urine of children; smoking by maternal caregiver	Emergency room and asthma clinic visits	Higher levels of cotinine in asthmatic children OR=1.9 (95% CI = 1.0, 3.4)	Similar cotinine levels in acute and nonacute asthmatic children

Source: Adapted from U.S. EPA (1993), Table 7-7

6.1.1.1 Epidemiologic evidence

Evans and colleagues (1987) analyzed data on 276 children from low-income families receiving care for asthma at outpatient clinics of several New York City hospitals. Information on ETS exposure was obtained during interviews of the parent or guardian and the child. Data on emergency room (ER) visits and hospitalizations were obtained by reviewing records for a one-year period, data on lung function were obtained during a random clinic visit occurring within one year after the interviews. Eight children who admitted to active smoking were excluded from the analysis, as were 77 other children with incomplete data. The relationships between the child's ETS exposure (as reported by the parent or guardian) and the outcome variables were analyzed by multiple regression techniques in which the influence of up to 34 potential confounders and effect modifiers were considered, including age, gender, ethnicity, several indicators of socio-economic status, indices of medical management, and an index of residential allergen and irritant exposure, among others. Evans and co-workers reported that ER visits were positively associated with reported ETS exposure ($p<0.01$). The mean annual frequency of ER visits among the children exposed to ETS in the home was 3.09 ± 0.40, while that for children not exposed was 1.83 ± 0.29. Thirty-nine percent of children from nonsmoking homes made no ER visits, compared with 29% of children from households with smokers. In addition, 13% of children from nonsmoking homes made four or more ER visits, compared with 32% of children from smoking households.

Evans *et al.* also reported, however, that ETS exposure was not associated with either hospitalizations or with percent predicted lung function. While ostensibly inconsistent with the ER results, there were relatively few hospitalizations during the period of observation (191 children x 0.20 (mean) hospitalizations/child/yr $\approx$ 38), resulting in a low power to detect an effect. Furthermore, to the extent that nondifferential misclassification of exposure occurred (or that some smokers may have reported that they were nonsmokers), this could bias the analysis against finding an effect. (Either of these types of misclassification of exposure would also tend to diminish the reported relationship between ETS exposure and ER visits.) The report does not provide enough information to evaluate the lack of association of ETS exposure and lung function. The protocol for pulmonary function test (PFT) administration is not well described; for example, it is not clear whether any children were experiencing an asthma flare when tested. Here also misclassification of exposure status could also create a bias against finding an association.

More recently, Chilmonczyk and colleagues (1993) undertook a study of similar design to that of Evans *et al.*(1987), using more sensitive indicators of asthma exacerbations (review of medical records at a large allergy/asthma clinic) and of ETS exposure (measurement of urinary cotinine at enrollment in addition to parental questionnaire). Cotinine is the major metabolite of nicotine, and is a good integrated indicator of recent ETS exposure (1-2 days; See chapter on *Exposure Measurements and Prevalence*). Review of medical records was done by observers blinded as to the children's ETS exposure status. Of the 199 children (aged 8 mos. to 13 yr, mean $\approx$ 7.5 yr) enrolled in the study, 145 were old enough to undergo pulmonary function testing. Whether assessed by urinary cotinine or by parental reporting, ETS exposure was found to be associated with increased frequency of asthma exacerbations in a dose-dependent manner. Using multiple regression techniques that adjusted for the child's age, gender, day-care attendance, the mother's age and educational level, the investigators reported relative risks for the highest versus the

lowest exposure categories of 1.7 (95% CI = 1.4-2.1) for exposure assessed by cotinine and 1.8 (95% CI = 1.4-2.2) for parent-reported exposure. Pulmonary function tests reported as percent predicted FEV_1 (forced expiratory volume in one second -- a measure of lung volume and central airway caliber) and FEF_{25-75} (expiratory flow during the middle half of a forced vital capacity (FVC) maneuver -- an indicator of the caliber of the more peripheral, mid-sized to smaller airways) were decreased with increased ETS exposure in a dose-dependent manner, with urinary cotinine as the exposure indicator.

In this investigation, parental reports of no ETS exposure were consistent with the cotinine results 86% of the time, while the concordance of reported exposure and cotinine measurements was 77%. Henderson *et al.* (1989) have previously shown that cotinine levels in preschool children tend to be stable over at least a four-week period, presumably due to regular daily patterns of ETS exposure. Ogborn *et al.* (1994) reported similar findings in children aged 3 to 11 (see below). To the extent that the single urinary cotinine measurement in the study by Chilmonczyk and colleagues was an accurate reflection of longer-term exposure, this study suggests an exposure-related chronic effect on exacerbations of pediatric asthma and on indices of lung function.

Murray and Morrison (1989) examined 419 children aged 1 to 17 attending an allergy clinic in Vancouver, British Columbia. At the initial visit a trained interviewer administered a standardized questionnaire to the parent and the patient containing questions regarding the child's asthma history, symptoms and medication use, other respiratory illnesses, and a variety of potential residential exposures (ETS from one or both parents, whether a woodstove was used for home heating or a gas stove for cooking, the presence of cats or dogs). The children were asked privately if they were themselves active smokers: the four that admitted to this were excluded from the analysis. The investigators created an asthma severity score based on questionnaire responses. In addition, the patients had allergy testing (by skin prick), spirometry (for those ≥ 6 year old), and an examination of bronchial reactivity to histamine (in children ≥ 7 year old). Children of smoking mothers (n=92) had more severe asthma than children of nonsmoking mothers (n=322), as evidenced by an increased asthma score, greater airway reactivity, as well as decreased FEV_1 and FEF_{25-75} (for all these differences, $p<0.01$). These results were driven by the effects observed in boys; for girls, only the asthma severity score was significantly increased with smoking versus nonsmoking mothers.

Murray and Morrison found that differences between asthmatic children of smoking versus nonsmoking mothers became more pronounced with increasing age (or duration of exposure). In multivariate regressions of these indices of severity on several independent variables (recent respiratory infection, recent bronchodilator use, positive skin prick test, presence of gas stove or wood stove, and the number of cigarettes smoked at home by either parent), stratified on age and/or gender, maternal smoking repeatedly emerged as one of the two strongest predictors of asthma severity. Paternal smoking was generally without effect.

The results of this study were consistent with earlier publications by the same investigators using subsets of this study population (Murray and Morrison, 1986 and 1988). In an analysis of 240 subjects for whom data were collected as described above (for the 1989 publication), Murray and Morrison found a highly significant association between indices of increased asthma severity (here

limited to airway reactivity, FEV_1, and FEF_{25-75}) and maternal smoking, with no such associations observed for paternal smoking. Hypothesizing that the children's asthma would be exacerbated during the colder, wetter months (when homes would be kept more tightly closed and children would spend more time indoors, thereby increasing the intensity of ETS exposure), they stratified the analysis by season (October through May versus June through September). They observed no differences in any of the above indices between children of smoking and nonsmoking mothers during the dry season, but found highly significant differences in FEV_1, FEV_{25-75}, and airway reactivity during the wetter months. Moreover, during the wet, but not the dry, season there was evidence of an exposure-response relationship between the number of cigarettes smoked by the mother in the home with each of these indices. These relationships were corroborated by multiple regressions of FEV_1, FEF_{25-75}, and airway reactivity on age, duration of asthma, gender, recent respiratory infection, recent medication use, positive skin allergy test, family history of asthma, presence of pets, heating type, presence of a gas range, number of siblings, and parental smoking.

More recently, Murray and Morrison (1993) expanded their analysis to include 807 nonsmoking asthmatic children and adolescents meeting the same eligibility requirements and for whom similar data were collected as in these authors' prior reports. In this analysis, they compared indices of asthma severity in children first attending the asthma clinic before July 1986 with those attending afterward. They reported that, among children with at least one smoking parent, reported daily exposures to cigarettes smoked in the same room were markedly lower after 1986 (3.4 after versus 6.6 before for smoking mothers ($p=0.005$) and 2.0 after versus 4.6 before for fathers ($p=0.001$)). Concomitant with this apparent decline in exposure, children of smoking parents entering the study after July 1986 had asthma that was less severe than those entering earlier, as manifested by significant improvements in the asthma score, FEV_1 and FEF_{25-75}. Among children of nonsmoking parents who enrolled after July 1986, the asthma severity score was not significantly different, but both FEV_1 and FEF_{25-75} were increased, though less so than among the children of smoking parents. Improvements in pulmonary function test values occurred regardless of the smoking status of either parent; however, a significant difference in the asthma severity score was observed only among the children of smoking mothers. Modeling the spirometric indices as a function of numbers of cigarettes smoked in the same rooms as the child(ren), controlling for several relevant covariates (age, gender, age of asthma onset), Murray and Morrison found that the differences among smokers' children across the time periods decreased, which would be expected if exposure to parents' smoking is one of the etiologic factors underlying the difference. Airway reactivity showed no marked differences in before/after comparisons within either group of children. In light of the significant improvement in the other indicators of asthma severity, the lack of a significant change in airway reactivity was unexpected; the authors had no ready explanation for this anomaly other than that the persistent hyperresponsiveness of these asthmatics' airways might not have been affected by recent decreases in exposure to parental ETS.

O'Connor *et al.* (1987) examined the relationship between parental smoking and airway reactivity in 286 children, aged 6 to 21 yr (mean ≈ 13 yr), in East Boston. Airway responsiveness was assessed by measuring FEV_1 before and after challenge with subfreezing air. Of the 21 asthmatic study subjects, those with smoking mothers showed a greater reduction in FEV_1 in response to cold air challenge than did those with nonsmoking mothers ($24 \pm 3.3\%$ vs $11.9 \pm 4.8\%$,

respectively; p = 0.07). In multiple linear regression models examining cold air-induced change in FEV_1 as the dependent variable in relation to nine putative independent variables, maternal smoking emerged as a significant (p = 0.02) predictor of ΔFEV_1, after adjusting for predicted FEV_1. In a stepwise multiple linear regression, maternal smoking and predicted FEV_1 were the only two variables to enter the model. Paternal smoking was unrelated to bronchial responsiveness in any analysis. The small sample size of the asthmatic children and adolescents in this study limits both the statistical significance and the generalizability of the findings. Nevertheless, the trend observed in this investigation is consistent with the results reported by Murray and Morrison (1989).

Household ETS exposure may affect severity of asthma in adults as well as children. Jindal (1994) investigated several measures of respiratory morbidity in 200 never-smoking adult asthmatics, aged 15 to 50, attending an outpatient chest clinic in India. Information on ETS exposure and on various indices of asthma control during the preceding year were obtained by questionnaire during a clinic visit. ETS-exposed participants (n = 100) were defined as those who reported a minimum of one hour exposure/day, or seven hour/week, for at least one year. Indices of asthma control included: lung function measurements, the use and number of maintenance bronchodilator medications, requirement for corticosteroids (presumably orally administered, though this is not clear from the article), numbers of visits to the emergency department, admissions to hospital, number of acute episodes, and number of times that the patients used parenterally administered (*i.e.*, via injection) asthma medications at home (reportedly a common practice in the study area). Pulmonary function testing was done within 24 hours of the clinic visit at which the questionnaire was administered. In comparison with a nonexposed group of 100 patients, the ETS-exposed group showed significantly lower forced expiratory lung function indices (FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$). In addition, though the numbers of patients in the two groups did not differ with respect to most of the morbidity measures, the ETS-exposed group included significantly more patients on maintenance bronchodilator therapy and corticosteroids required to control symptoms. When expressed on a per-patient-per-year basis, however, all the indices in the ETS-exposed group were significantly higher, except for the numbers of hospital admissions and weeks of bronchodilator use per patient. Although not conducted or analyzed as meticulously as the investigation by Chilmonczyk and colleagues (1993) (above), this report suggests that regular ETS exposure may affect control and severity of asthma in adults as well as children.

The above reports support the existence of an association of chronic or repeated ETS exposure with severity of asthma measured by a variety of indices. In several epidemiologic studies, ETS has been implicated as a risk factor for exacerbation of asthma, measured as increases in symptoms, medication use, and clinic or emergency room (Evans *et al.*, 1987; Chilmoncyzk *et al.*, 1993; Jindal *et al.*, 1994; Ostro *et al.*, 1994 (see below)). Airway responsiveness, one indicator of asthma severity, tends to be increased in asthmatic children whose mothers smoked in comparison with those with nonsmoking mothers (O'Connor *et al.*, 1987; Murray and Morrison, 1989). The results of controlled chamber investigations suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which provides experimental support for the epidemiological observations (Menon *et al.*, 1992). Increased airway responsiveness facilitates bronchoconstriction (and the concomitant symptoms of chest tightness, wheeze, and difficulty breathing) in response to respiratory irritants, such as ETS (NRC, 1986).

The above findings support the assessment articulated by the U.S. EPA that there is sufficient evidence to support the inference of a causal relationship between ETS exposure and "additional episodes and increased severity of asthma in children who already have the disease."

Whether acute ETS exposure can precipitate a specific asthma flare is not so clear-cut, however. Ehrlich *et al.* (1992) undertook a case-control study of 72 children visiting the emergency room (ER) for their asthma, 35 children attending an asthma clinic who were not acutely ill, and 121 nonasthmatic control children. ETS exposure was assessed by questionnaire and by urinary cotinine/creatinine ratios (CCR). Using a cut-point of 30 ng cotinine/mg creatinine to distinguish exposed versus unexposed children, they found no difference in recent ETS exposure between asthmatics recruited from the ER and those from the clinic. In contrast, the ETS exposure odds ratio for all asthmatics versus controls was 1.9 (95% CI = 1.04 - 3.35). The mean CCR in the acute asthmatics (46.2 ± 98.3) was greater than that in the nonacute asthmatics (38.5 ± 74.1), but this difference was not statistically significant. From the questionnaire responses, there was no significant difference between acute and nonacute asthmatics in relation to maternal smoking, whereas the exposure odds ratio for asthmatics versus controls was 2.0 (95% CI = 1.1 - 3.4). This investigation suggests that ETS exposure is a risk factor for clinical asthma but, in this study population, may not have been a significant precipitant of asthma flares serious enough to warrant a visit to the ER. However, the investigation by Ehrlich *et al.* cannot adequately address the latter issue because of limited statistical power (<50% probability of detecting a 2-fold exposure difference between acute and nonacute asthma), coupled with the likelihood that the children recruited from the clinic had more severe asthma (with 80% on daily asthma medication vs. 36% of the ER patients).

Ogborn and colleagues (1994) also investigated whether there was an association between exacerbations of asthma and acute exposure to ETS. Data consisted of parental responses to detailed ETS exposure questionnaires and measurements of urinary cotinine obtained from children, aged 3 to 11, who were seen during a visit to the ER or primary-care clinic during an acute asthma flare and at a follow-up clinic visit after the flare had subsided. The investigators found no significant difference between mean urinary cotinine values (± standard deviation) at the acute versus the well visit (81 ± 62 ng/ml and 77 ± 57 μg/ml, respectively). Similarly, the mean CCRs at the acute versus the well visits were 93 ± 109 ng/ml and 97 ± 87 ng/ml, respectively. (Note that the mean CCR values in this study are at least twice as great as those reported in the Ehrlich *et al.* (1992) study, suggesting heavy ETS exposure.) In this population, the prevalence of household smoking was remarkably high (77% overall, and 63% among the children's mothers). However, this investigation is also limited by low power: the sample size of 56 had a power of 0.80 ($\alpha = 0.05$) to detect the change in CCR expected to result from a 20-cigarette per day change in ETS exposure. In other words, this study would have the power to detect a difference equivalent to household smokers' (or other sources of ETS exposure) reducing their consumption of cigarettes by one pack a day, over a several-week interval, with no concerted smoking cessation intervention. Thus, this underpowered study cannot address the issue of whether acute ETS exposure can provoke an exacerbation of asthma.

However, the study by Ogborn *et al.* does provide additional interesting information about the stability of CCRs over time. The acute and well visits of these children were separated by

approximately three to four weeks (detailed information on the timing of the visits is not provided in the report). Among the children reported to be "exposed" to ETS, the mean CCR was 105 ± 119 ng/ml at the ER visit and 105 ± 85 ng/ml at the follow-up visit, which is consistent with regular ongoing exposures. In addition, this study provides evidence that parents may under-report ETS exposure. Using a urinary CCR of 30 ng/mg as a cut-point for recent ETS exposure, the mean CCR levels in the children reported not to have been exposed at the acute and well visits were 41 ± 30 ng/ml and 83 ± 100, respectively.

There is suggestive recent evidence that ETS exposure may elicit acute symptoms in adults. Ostro *et al.* (1994) investigated the relationships between exposures to indoor combustion products and daily symptoms in a population of adult asthmatics residing in Denver, Colorado. This study included 164 subjects, many of whom had moderate to severe asthma, and some of whom experienced respiratory infections and asthma flares during the period of observation. This investigation also had more than 10,000 observations, which afforded substantial statistical power to detect associations with indoor exposures, including ETS. Both symptom and exposure data were recorded by the study participants in an intake questionnaire and in daily diaries over a three-month period. In multiple logistic regression models corrected for serial correlation and repeated measures, these investigators reported an odds ratios of 1.61 (95% CI = 1.06 - 2.46) for restricted activity days in relation to ETS exposure. They also reported significantly increased odds ratios for the occurrence of moderate to severe cough and shortness of breath, which were still elevated but no longer significant after correction for autocorrelation. However, having a smoker in the home during the course of the study corresponded to an odds ratio of 2.05 (95% CI = 1.78 - 2.40) for increased daily moderate to severe shortness of breath, suggesting a relationship of chronic exposure to acute symptoms as well.

The studies reviewed in this section support the previous finding by the U.S. EPA (1992) that there is "sufficient evidence…that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease." There is suggestive evidence that ETS exposure may exacerbate adult asthma. The U.S. EPA (1992) estimated that ETS exposure potentially could exacerbate pre-existing asthma in approximately 20% of 2 to 5 million children, *i.e.*, in 0.4 to 1 million children. Assuming that 12% of those children reside in California would result in estimates of 48,000 to 120,000 asthmatic children who could experience a worsening of their condition due to exposure to ETS.

6.1.1.2 Evidence from chamber studies

Several chamber studies have investigated potential relationships between controlled exposure to ETS and lung function and airway reactivity in asthmatic subjects. The results of these investigations are summarized in Table 6.2. Experimental exposure of human volunteers to various pollutants under controlled laboratory conditions can provide useful pathophysiological information. The principal advantages of this methodology over epidemiological studies is that exposure to the pollutant(s) of interest can, in theory, be precisely measured, and thus exposure-response relationships determined. While exposure conditions can also be controlled in animal experiments, the obvious strength of human chamber studies is that no cross-species extrapolation is required. On the other hand, microscopic or biochemical examination of pollutant-induced tissue damage is more limited in humans by both ethical and practical considerations. However,

controlled human exposures are also subject to the following structural limitations: (1) only short-term responses to relatively brief exposures (*i.e.*, minutes to hours) can be evaluated; (2) there is often limited statistical power to detect effects, due to the typically small number of subjects; (3) controlling the experimental conditions may result in failure to capture effects found in complex real-world exposures; (4) multiple selection biases in recruiting volunteers reduce the generalizability of such studies (*e.g.*, systematic exclusion of people with a history of recent respiratory infection; relatively few studies of children, adolescents or other potentially susceptible subgroups). It should be emphasized, however, that these limitations all tend to underestimate pollutant effects. Given the potential shortcomings of such investigations, negative findings may in some cases reflect the constraints of study design more than biological reality.

In controlled exposure studies, volunteer subjects are exposed to one or more pollutants through a mouthpiece (oral breathing only) or in a chamber (oronasal breathing). ETS-related studies of asthmatics have mainly been conducted in exposure chambers with resting subjects. Data collected usually have included graded respiratory symptoms and a variety of indices of pulmonary function, such as the amount of air a subject can exhale in one second after a deep inspiration (FEV_1) or the lung's resistance to airflow (airway resistance (R_{aw}) or specific airway resistance (SR_{aw})). Several studies of asthmatics involving ETS exposures have also examined airway responsiveness (also known as bronchial reactivity) (described below).

Chronic airway inflammation and episodic, reversible bronchoconstriction are hallmarks of asthma. Inflammation is associated with bronchial hyperreactivity or hyperresponsiveness, which refers to an exaggerated tendency of the airways to constrict when exposed to respiratory irritants or other substances. Airway hyperresponsiveness (AHR) is also observed in many persons with emphysema and bronchitis and in otherwise healthy individuals during and after respiratory tract infections and after exposure to respiratory irritants such as ozone. In general, however, such reactivity is markedly greater in asthmatics compared with nonasthmatics. Airway responsiveness to numerous stimuli can be measured in clinical studies. Methods used to induce and measure nonspecific bronchial reactivity in asthmatics include exercise or hyperventilation with cold or dry air, or inhalation of pharmacological agents (*e.g.*, histamine or methacholine). Although these pharmacological agents also cause bronchoconstriction in healthy individuals, asthmatic airways constrict at much lower exposure concentrations. AHR creates the potential for a flare or exacerbation of asthma, with heightened bronchial responses to other nonspecific airborne irritants.

The series of studies conducted at Tulane University (Stankus *et al.* 1988; Menon *et al.*, 1991 and 1992) suggest that a substantial fraction of asthmatics with self-reported sensitivity to ETS also appear to demonstrate susceptibility by more objective means of assessment (tests of lung function and airway responsiveness). While such susceptible individuals have increased baseline AHR (as measured by methacholine challenge testing), nonspecific airway reactivity does not fully explain this sensitivity, since other asthmatics with increased AHR do not show marked reactions to ETS inhalation challenge. Although the physiologic basis for susceptibility is not well understood, the effects of exposure on such ETS-reactive and nonreactive individuals appear to be reproducible, suggesting the existence of intrinsic individual characteristics (Stankus *et al.*, 1988; Menon *et al.*, 1991). Though these acute studies cannot replicate exposure conditions

Table 6-2: Controlled Exposures of Asthmatic Subjects to ETS

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Shephard *et al.* (1979)	14 mild to moderate asthmatics (aged 19-65; 9M/5F).	2-hr. mechanical smoke generation in a small room. Estimated TSP range = 2-4 mg/m^3; CO average estimated to be 24 ppm.	Sl. ↓TLC and sl. ↑FVC for ETS vs. sham exposures. 4 "sensitive" subjects did not differ from others' responses, except for sl. ↑FEV_1.	Not measured.	3/14 SOB; 5/14 wheeze; 6/14 chest tightness; 5/14 cough. Symptoms reported ranged from trace to moderate severity.	Regular anti-asthma not withheld prior to test ($^{13}/_{14}$ subjects). One or more subjects may themselves have been smokers. Statistical methodology not described. Exposure concentrations not measured during experiment.
Knight and Breslin (1985)	6 patients with "mild to moderate asthma".	1 hr. Mechanical cigarette smoke generation.	Mean decline from baseline of 11% on ETS exposure vs. an increase of 4% on control day.	↑ with histamine on exposure vs. control days.	3/6 - ↑ chest tightness; 2/6 - wheeze.	Subjects and methods not well described. Exposure not well characterized. Statistical approach not described.

Table 6-2: Controlled Exposures of Asthmatic Subjects to ETS (continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Menon *et al.* (1991)	15 self-reported "smoke-sensitive" asthmatics, including 6 "reactors" and 9 "nonreactors" to prior ETS challenge (aged 25-51, 3M/12F); 15 self-reported "smoke-sensitive" controls with upper respiratory symptoms on exposure to ETS (aged 21-48; 5M/10F). All subjects were atopic.	2- or 6-hr. chamber exposure, with mean TSP = 1145±325 $\mu g/m^3$, mean nicotine = 205±54 $\mu g/m^3$. "Reactors" also subject to "sham" exposure in chamber without ETS. "Reactors" subsequently re-tested after pre-treatment with a bronchodilator (albuterol), an anti-inflammatory medication (cromolyn sodium) or both.	5/6 "reactors" showed >20%↓ FEV_1 after 1-2 hr. exposure. None showed ≥20% FEV_1 after sham exposure. The 6th "reactor" showed >20% ↓ FEV_1 after 6 hr. exposure. No "nonreactors" or controls experienced significant declines in FEV_1 in either 2-hr. or 6-hr. ETS exposures. Pre-treatment with drugs blocked ↓FEV_1 (p=0.06 for single drug; p=0.03 for combination)	Not tested.	Respiratory symptoms not reported. 2/3 of both asthmatics and nonasthmatics reported severe odor, nasal and eye irritation.	Reproducible reactions of "reactors" and "nonreactors" to ETS challenges separated by 2 yr. suggests existence of susceptible subgroup of asthmatics. All "reactions" required at least 1 hr. of exposure. Negative results of sham exposure of reactors reduces likelihood of "stress" or artifactual explanation of results.
Menon *et al.* (1992)	31 "smoke-sensitive" asthmatics (11M /20F); 39 "smoke-sensitive" controls with upper respir symptoms (17M /22F). All subjects aged 12-50; atopic.	4 hr. chamber exposure, with mean TSP = 1266 ± 283 $\mu g/m^3$, mean nicotine = 226 ± 49 $\mu g/m^3$.	5/31 asthmatics showed ≥ 20% ↓ FEV_1 vs. 0/39 controls.	↑ with methacholine at 6 hr. (32% vs. 18%) and 24 hr. (29% vs. 10%), for asthmatics vs. controls.	Not reported	Prolonged AHR reported in 13% of asthmatics (2 wk. post-ETS) and in 2 subjects (1 asthmatic and 1 control) for up to 8 wk. post-exposure. Some of these may also have had ETS exposure at home or work.

Table 6-2: Controlled Exposures of Asthmatic Subjects to ETS (continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Wiedemann (1986)	9 mild, asymptomatic asthmatics (aged 19-30; 5M/4F). Not selected on basis of smoke sensitivity.	1 hr. chamber exposure, with mean CO = 40-50 ppm. Subjects allowed to wear goggles.	Sl. (2%) ↓FVC ($p = .01$). No change in FEV_1	Sl. ↓ with methacholine immediately post-exposure.	3/9 - mild cough; eye and nasopharyngeal irritation.	No test of delayed AHR. Sl. ↓ AHR of uncertain clinical significance.
Oldigs *et al.* (1991)	11 mild asthmatic children (aged 8-13, 10M/1F); not selected on basis of smoke sensitivity.	1 hr. chamber exposure, with mean TSP = 2743 ± 348 $\mu g/m^3$, mean nicotine = 397 ±78 $\mu g/m^3$, mean CO = 20.5 ± 0.5ppm. During control exposure, mean TSP=17 ± 57 $\mu g/m^3$, mean CO = 0.1 ± 0.3 ppm.	No significant difference before and after ETS exposure in FEV_1 or SRaw.	No significant differences with histamine challenge before and after ETS exposure.	Only eye irritation significantly different during ETS vs. control exposure.	No test of delayed AHR. 9/11 were on chronic asthma therapy, which could dampen responses to ETS. Also, 6/11 were chronically exposed to household ETS, which may affect acute response in an experimental setting.
Dahms *et al.* (1981)	10 asthmatics (aged 18-26), 5 of whom were smoke-sensitive, 10 healthy controls (aged 24-53)	1- hour chamber exposure, CO estimated at 15-20 ppm based on ↑ in subjects' carboxyhemoglobin	FVC↓ 20%, FEV_1 ↓21.4%, $FEF_{25-75\%}$ ↓19.2 % in asthmatics; vs. no change to SC. ↑ in these indices among controls. Progressive linear decrease in asthmatics' PFTs with increasing duration of exposure.	Not tested.	All subjects had similar degrees of eye and nasal irritation.	Smoke exposure concentrations not measured directly. No individual-level data reported

Table 6-2: Controlled Exposures of Asthmatic Subjects to ETS (continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Stankus *et al.* (1988)	21 smoke-sensitive asthmatics (aged 21-50; 5M/16F); 19/21 atopic.	2 hr. "low-level" exposure (mean particle concentration = 852 ± 52 $\mu g/m^3$, mean CO = 8.7 ± 1.7 ppm, mean nicotine = 180 ± 44 $\mu g/m^3$) for 2 subjects. All others had 2 additional hr. "high-level" ETS exposure (mean particle concentration = 1421 $\pm$300 $\mu g/m^3$, mean CO=13.3 $\pm$ 3.2 ppm, mean nicotine = 439 121 $\mu g/m^3$).	7/21 showed $\downarrow$ FEV_1 exceeding 20%, maximum decrement $\approx$ 50%.	Not tested.	Cough, dyspnea and/or chest tightness in all subjects with $\downarrow$ FEV_1 > 20%. Eye irritation in all subjects; nasal congestion and headache in several.	"Reactors" and "nonreactors" showed similar responses to subsequent ETS challenge. Response to ETS not related to allergy to tobacco leaf extract.

Table 6-2: Controlled Exposures of Asthmatic Subjects to ETS (continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Magnussen *et al.* (1993)	13 atopic children with asthma (aged 8-13, 8M/5F)	1 hr. (54 min. at rest and 6 min. bicycle exercise) mean particle concentration = 3,197± 665 $\mu g/m^3$, mean CO concentration =20.2± 0.7 ppm). Goggles worn to prevent eye irritation.	Transient $FEV_1\downarrow$ (7.2 % ETS vs. 3.2% in ambient air).	ETS exposure did not affect exercise-induced broncho-constriction.	No significant symptom difference between ETS and clean air exposures.	No test of delayed AHR. 7/13 exposed to ETS at home. Poor reproducibility of symptoms between duplicate exposures.
Danuser *et al.* (1993)	10 healthy and 10 subjects with hyper-reactive airways (aged 24-51; 8M/12F) 5 of latter group had asthma, 3 additional subjects had symptoms suggestive of asthma.	Serially increasing 2-min. exposures to ETS delivered via mouthpiece. CO concentrations = 0,2,4,8,16 and 32 ppm ± 5%. Subjects wore nose-clips during exposures.	No effect in healthy subjects. 9/10 with AHR had $\downarrow FEV_1$, 5/10 had $\downarrow FEV_1 >$ 10%. Mean $\downarrow FEV_1$ = –6.5% at 2 ppm CO and –8.7% at 32 ppm CO. ANOVA showed highly significant ($p<0.0001$) effect of ETS on FEV_1, FVC and MEF_{50}.	Not tested.	Weak symptomatic responses, though dyspnea, cough and chest tightness increased at higher ETS concentrations.	Small likelihood of "suggestibility" because of mode of ETS delivery. FEV_1 showed decline at 2 ppm CO and a response plateau at higher concentrations. AHR to methacholine and pre-exposure pulmonary function test values did not fully predict response to ETS.

Sl. = slight, TSP = total suspended particulates, CO = carbon monoxide, TLC = total lung capacity, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, SOB = shortness of breath, AHR = airway hyperresponsiveness, SRaw = specific airway resistance, $FEF_{25-75\%}$ = forced expiratory flow during middle half of expiration, ANOVA = analysis of variance

experienced by free-living subjects, the findings of increased AHR support the epidemiological studies described earlier, which indicate that repeated household ETS exposures tend to result in worse control of asthma.

Most of the ETS inhalation chamber studies show slight-to-moderate, transient effects on lung function in at least some of the study subjects. In several studies, participants experienced decrements in lung function exceeding 20%, which would be considered clinically significant, particularly in conjunction with the occurrence of lower respiratory symptoms such as chest tightness, dyspnea, and cough. To the extent that subjective symptoms of asthma were reported, clinically meaningful respiratory symptoms were identified in some participants in several studies (Knight and Breslin, 1985; Dahms, 1981, Stankus *et al.*, 1988, Shephard *et al.*, 1979); however, this was clearly not a universal finding (Magnussen *et al.*, 1993, Oldigs *et al.*, 1991). AHR occurring after ETS exposure was also reported inconsistently in these studies; nevertheless, the only studies that examined delayed AHR at times that would be likely to detect the effects of an inflammatory response did find significant ETS-associated increases (Menon *et al.*, 1991 and 1992).

The controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole. As noted above, however, general design constraints in such studies militate against finding effects, *e.g.*, small sample size, systematic exclusion of potential participants who have recently been ill or those with brittle asthma, acute exposures only. Each of these studies has one or more weaknesses in design or analysis; thus, neither individually nor collectively can these investigations definitively address the issue of whether acute ETS exposure can precipitate an asthma flare. For instance, in Shephard *et al.* (1979), anti-asthma medications were not withheld prior to the exposures in 13/14 participants, which would be likely to dampen any potential effects of ETS. Several investigations involved fewer than a dozen subjects (Knight and Breslin, 1985, Wiedemann, 1986; Oldigs *et al.*, 1991); all but two of the remaining studies had fewer than two dozen subjects. In at least two studies (Oldigs *et al.*, 1991; Magnussen *et al.*, 1993), the participants were also regularly exposed to ETS at home, which could affect their responses in an acute experimental setting. Menon *et al.* (1991) indicated that at least one hour of exposure was needed to elicit respiratory responses, even among their ETS-sensitive subjects. Several of the chamber studies (including most of the "negative" ones) involved exposure to ETS that was limited to only one hour (Knight and Breslin, 1985, Wiedemann, 1986; Oldigs *et al.*, 1991, Dahms, 1981, Magnussen *et al.*, 1993, Danuser *et al.*, 1993). Moreover, there is considerable variability among asthmatics with respect to susceptibility to airborne irritants, including ETS. For instance, adult asthmatics vary at least seven-fold in their susceptibility to the bronchoconstrictive effects of sulfur dioxide, which is probably the most well-studied respiratory irritant in relation to asthma (Horstman *et al.*, 1986). Thus, even apart from differences in study design and experimental conditions, investigations of the effects of acute ETS exposure in asthmatics would be expected to produce variable results.

Finally, one criticism of ETS chamber studies has been that the characteristic odor and mucous membrane irritation make it difficult to blind the participants to the nature of the exposure (ETS vs. clean air). This in turn is hypothesized to result in psychological suggestion as a cause of observed symptoms, changes in lung function, and so forth (Witorsch, 1992). Similarly, it has been argued that the physical conditions of participating in an inhalation challenge study create

"stress" to which any positive results might be attributed (Witorsch, 1992). As for the latter observation, the use of control exposures, control subjects or both are intended to provide a basis for "control" for whatever stresses are associated with the experimental procedure. Suggestibility related to the lack of blinding may theoretically augment symptomatic and physiological responses, but experimental evidence suggests that, if present, its influence is weak. In the study by Danuser *et al.* (1993), the subjects wore noseclips and had the ETS administered by mouthpiece, essentially blinding them to the differences in concentration of ETS delivered. Yet most of the symptomatic responses of the subjects with AHR, though not clinically severe, appeared to be dose-related, which would be difficult to attribute to suggestion. Urch *et al.* (1988) investigated the role of suggestibility in 40 nonsmokers, including 16 asthmatic and 24 nonasthmatic adults. Participants were exposed in an exposure chamber on separate occasions for 65 minutes to clean air ("sham"), moderate or heavy smoke (17 and 31 ppm carbon monoxide, respectively). Though they viewed a bank of burning cigarettes outside the chamber on all occasions, the smoke was diverted during the sham experiment. These investigators reported, among other results, the occurrence of significant dose-related symptoms in asthmatics and nonasthmatics and a dose-response relationship for several measures of lung function. They also administered a battery of psychometric tests to assess the subjects' suggestibility, and found little correlation between physiological changes and indices of suggestibility. Assuming the subjects were unable to distinguish between the moderate and heavy smoke concentrations, Urch *et al.* concluded that the dose-response relationships were more likely of physiological than psychological origin, although the latter may have played a minor role in the observed responses.

In summary, although the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure. The physiological responses observed in these investigations appear to be reproducible in both "reactors" and "nonreactors". It is unlikely that the physiological and symptomatic responses reported are due exclusively to either stress or suggestion.

6.1.2 Respiratory Infections (children)

Infections of the respiratory tract are the most common acute illness of childhood. Apart from the morbidity (and occasional mortality) attributable to respiratory infections, they also represent risk factors for asthma (both induction and exacerbation of existing disease) and possibly other chronic respiratory effects in later life (Burrows *et al.*, 1977; Gold *et al.*, 1989; Henderson *et al.*, 1992; Schroekenstein and Busse, 1988). The relationship of parental smoking to the risk of respiratory infection has been extensively investigated. It has been clearly established in nearly two dozen reports reviewed by the NRC (1986), the Surgeon General (1986) and the U.S. EPA (1992) that ETS exposure increases the risk of acute lower respiratory disease in young children by 1.5 to 2-fold.

The estimates of the magnitude of the effect of household ETS exposure on respiratory infections are remarkably consistent among the many studies that have examined this relationship. The effects are most marked in infants and toddlers, and are often not detectable in school children, who may be less exposed than younger children or who may have developed immunity against many respiratory pathogens. Several studies noted the existence of a dose-response relationship, where dose was measured by the number of cigarettes smoked in the household. In studies

conducted mainly in Europe and North America, maternal smoking has repeatedly been found to bear a stronger relationship to respiratory illness than paternal smoking. This is likely to be due to the greater amount of time spent by mothers than by fathers with young children, enhancing the frequency and intensity of ETS exposure, strengthening the inference of a causal association. However, the series of reports by Chen *et al.* (1986, 1988, 1989), which involved cohorts of infants with nonsmoking mothers, also found dose-response relationships with paternal smoking. The reviews by the U.S. EPA, NRC, and the Surgeon General all noted that most of these studies, while not free of all sources of bias, had adjusted for many identifiable confounding variables and found that the ETS effects were independent of sex, race, maternal age, socio-economic status (SES), residential crowding, and number of siblings. In some studies, breast-feeding had a protective effect, as did day-care attendance, the latter presumably by decreasing exposure to parental ETS. Low birth weight increased susceptibility to ETS effects (U.S. EPA 1992). As a group, these nearly two dozen investigations are quite consistent and provide convincing evidence of an increased risk of lower respiratory illness in young children.

The discussion of the relationship between ETS exposure and pediatric respiratory illness has been adequately addressed in the reviews by the NRC, the Surgeon General, and the U.S. EPA., and therefore a *de novo* analysis of the primary literature has not been undertaken. More recent published investigations support the conclusions articulated in these reviews. For example, Chen (1994) reported increased risks of hospitalization for respiratory illness during the first 18 months of life in China as follows: ORs = 2.91 (95% CI = 1.41 - 6.01) and 4.48 (95% CI = 2.07 - 9.73) among low birth weight infants exposed to light and heavy household smoking, respectively, and 1.40 (95% CI = 0.96 - 2.03) and 1.61 (95% CI = 1.08 - 2.41) for similar exposures among children of normal birth weight. Similarly, Robertson (1994) found an ETS-associated increased risk of hospitalization (for respiratory and other causes) during the first six to ten months of life in a cohort of 1,877 infants in New Zealand (OR = 1.52, 95% CI = 1.08 - 2.14). In a prospective study of respiratory illness during the first two years of life in 836 Australian children, Douglas *et al.* (1994) reported that maternal smoking was associated with a significantly increased frequency of respiratory illness in the second, but not the first year of life. While each of these investigations has one or more methodological limitations, they are generally consistent with the reports discussed in the above-noted reviews. These and other recent studies support the conclusions stated in the reports by the NRC, the Surgeon General, and the U.S. EPA., that ETS exposure clearly confers an increased risk of acute lower respiratory disease in young children.

As noted above, ETS exposure in early childhood has been estimated to increase the risk of lower respiratory infection by 1.5 to 2-fold. On a national level, this magnitude of increased risk would correspond to 150,000 to 200,000 ETS-related cases of lower respiratory illness annually in children under 18 months of age (U.S. EPA, 1992). Noting that approximately 5% of patients with lower respiratory illness require hospitalization, the U.S. EPA estimated that 7,500 to 15,000 admissions to hospitals are attributable to ETS exposure each year in the U.S. These may be underestimates of effect, since the calculations on which they were based did not account for either exposure to paternal smoking or the likelihood of occurrence of repeated episodes of illness in regularly exposed children. If 12% of the population at risk resides in California, these estimates would correspond to 18,000 to 36,000 new cases of lower respiratory illness each year and 900 to 1,800 hospitalizations attributable to ETS exposure.

6.1.3 Otitis Media (children)

A number of studies, cited in the preceding subsections, link passive smoking with lower respiratory tract conditions in children. The relationship between ETS exposure and childhood upper respiratory tract conditions, particularly acute and chronic otitis media, constitutes a separate area of concern. This topic has been reviewed extensively by the Surgeon General's Office (U.S. DHHS, 1986), the NRC (1986), and the U.S. EPA (1992). This section briefly summarizes the findings of the above three reports, reviews those studies not included in the reports, and explores related evidence on pathophysiology.

6.1.3.1 Background/Definitions

Otitis media is the most commonly diagnosed problem in outpatient pediatrics in the United States today (Etzel *et al.*, 1992). In the context of this discussion, it is useful to consider the anatomy and physiology of middle ear disease before reviewing the data concerning ETS as a risk factor for otitis media. The middle ear communicates with the nasopharynx via the Eustachian tube. The Eustachian tube acts as a barrier to microorganisms originating in the pharynx, as a pressure equalization channel, and as conduit of drainage for secretions originating in the middle ear. Eustachian tube dysfunction of whatever etiology results in a sustained pressure differential between the middle ear and the surrounding atmosphere, with subsequent effusion of serous fluid into the middle ear. Alone, this condition is called "serous otitis media," and produces a sensation of fullness and temporarily decreased hearing. Should the serous fluid become infected (usually with bacteria), "acute otitis media" results, with pain, fever, and the potential for tympanic membrane (TM) perforation. Serious secondary complications (meningitis, mastoiditis) can also occur, as can a self-perpetuating cycle of acute and serous otitis media (Goycoolea, 1991). Chronic serous effusions, with or without intervening infections, may lead to a variety of complications, including mucoid effusion (so-called "glue ear") and stretching of the tympanic membrane ("incompetent TM" or "atelectatic TM"), each resulting in more sustained hearing loss than does simple serous otitis. Tympanic membrane perforation can result, not only in hearing loss, but also in the formation of a "cholesteatoma" -- an ingrowth of squamous cells from the exterior of the TM -- which, in turn, can expand and destroy the ossicles of the middle ear. Hearing loss, whether from sustained serous otitis media, mucoid effusion, atelectatic TM, TM perforation, or ossicle destruction due to cholesteatoma, can result in communication difficulties and educational impairment in children.

6.1.3.2 Epidemiologic Data

The Surgeon General (1986) and NRC (1986) reviewed five and the U.S. EPA (1992) an additional ten studies on ETS exposure in childhood and upper respiratory tract conditions. Twelve of these fifteen studies examined acute or chronic otitis media and/or middle ear effusions. These twelve studies included five case-control, four prospective, and three retrospective or cross-sectional investigations, and are summarized in Table 6.3, as well as in the above three reviews. In all but three of these 12 studies, statistically significant relationships between exposure and outcome were apparent.

The reports of both the Surgeon General and the U.S. EPA expressed concern regarding potential misclassification of exposures based solely upon historical measures. Two studies (Strachan *et*

al., 1989; Etzel *et al.*, 1992) used objective measures of ETS exposure (salivary and serum cotinines, respectively), and both found a statistically significant relationship between ETS exposure and outcome. Likewise, two studies (Iverson, 1985; Etzel *et al.*, 1992) employed periodic prospective screening for middle ear disease, thus eliminating differential utilization of medical services by parents as a possible confounder. Again, both of these studies found statistically significant associations between ETS exposure and middle ear disease.

Table 6.4 summarizes an additional ten epidemiologic studies not included in the above summary reports (the Surgeon General's Office, NRC, or U.S. EPA). Several of these additional studies were problematic with respect to their study designs. For example in the Kallail (1987) study, cases and controls were not subjected to the same screening procedures. In the Pönka (1991) study, parental reporting, rather than medical records or objective surveillance, was the index of disease outcome. Nevertheless, three of the studies reported nonsignificant positive associations between ETS and middle ear disease, five reported a significant relationship, and none reported a protective effect. None of these studies utilized biomarkers of ETS exposure. The one study that used an objective measure applied on a prospective basis (tympanometry) did report a slight, but nonsignificant association (Zielhuis, 1989).

6.1.3.3 Summary of Epidemiologic Data

The Surgeon General's report (U.S. DHHS, 1986) summarized the studies as "show[ing] an excess of chronic middle ear effusions and diseases in children exposed to parental smoke." The U.S. EPA (1992) report concluded that there was "good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS," but only "some evidence [for] acute middle ear infections" (acute otitis media). While the ten studies in Table 6.4 are collectively somewhat less supportive of an association between ETS exposure and middle ear disease than those previously reviewed by the Surgeon General's Office and the U.S. EPA, the study design of some of these studies was problematic.

Ten of the twelve studies reviewed by the Surgeon General's Office or the U.S. EPA reported statistically significant relationships between ETS exposure in the home and middle ear conditions in children. Of the additional ten studies reviewed here, five showed a statistically significant relationship, three showed excesses that did not reach statistical significance, and two "no relationship" (in one case without numbers being presented). Overall, no studies show a protective effect (such as would be expected in at least some studies if all findings were a product of random variation). Two of three studies involving objective prospective surveillance (tympanometry or insufflation otoscopy) showed statistically significant associations, and the third a nonsignificant excess of middle ear problems with ETS exposure. Both studies involving biomarkers of ETS exposure showed statistically significant relationships between exposure and outcome.

TABLE 6.3
STUDIES OF MIDDLE EAR EFFUSION (MEE) AND OTITIS MEDIA (OM) VS. ETS EXPOSURE REVIEWED BY THE SURGEON GENERAL (1986), NRC (1986), OR U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Kraemer, 1983	case-control	76 children admitted for ear surgery for persistent MEE compared with nonotologic surgical patients. OR for ear surgery and $\geq$ 2 smokers in home = 2.8 (95% CI = 1.1, 7.0).
Iverson, 1985	prospective	337 children age 0-7 years followed in day care for 3 months with periodic tympanometry. Prevalence rate for MEE significantly associated with parental smoking, as determined by questionnaire ($p < 0.05$).
Black, 1985	case-control	150 children referred for ear surgery for "glue ear" (secretory OM) matched with 2 controls each. Risk ratio for parental smoking = 1.64 (95% CI = 1.03, 2.61).
Pukander, 1985	case-control	264 cases of acute OM were compared with 207 non-OM outpatients aged 2 to 3 years. Significant trend in proportion of children with historical ETS exposure as a function of increasing number of lifetime OM episodes.
Fleming, 1987	retrospective	Phone interview of 449 households. For children under 5 years old, maternal smoking was significant risk factor for upper respiratory tract infection, but not otitis media, within 2 weeks preceding interview (OR = 1.1; p = 0.82 for OM).
Tainio, 1988	prospective	183 infants followed from birth to 2.3 years of age. Parental smoking was significant risk factor for $\geq$3 OM episodes (RR = 1.7; 95% CI = 1.1, 2.7). Also, a significantly higher proportion of parents of children with "recurrent" OM ($\geq$5 episodes) smoked ($p < 0.05$).

TABLE 6.3 (continued)
STUDIES OF MIDDLE EAR EFFUSION (MEE) AND OTITIS MEDIA (OM) VS. ETS EXPOSURE REVIEWED BY THE SURGEON GENERAL (1986), NRC (1986), OR U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Reed, 1988	cross-sectional	49 children with a prior history of either acute OM (n = 24) or another outpatient diagnosis (n = 25) were examined by tympanometry. OR for MEE and reported parental smoking = 2.31 ($p < 0.05$).
Hinton, 1989	case-control	115 children, age 2-11 years, admitted for ear surgery compared with 26 other ENT clinic patients and 36 children with non-otologic diagnoses. Borderline significant trend in parental smoking comparing surgical to clinic to nonotologic patients ($p=0.06$).
Teele, 1989	prospective	877 children observed from birth to one year of age, 698 to age 3, and 498 to age 7. Parental smoking was significant risk factor for acute OM in children under age one year only.
Strachan, 1989	cross-sectional	Tympanometry and salivary cotinine samples obtained on 872 school children aged 6.5 to 7.5 years. Significant trend in OR for abnormal tympanogram (MEE) as a function of increasing salivary cotinine level.
Takasaka, 1990	case-control	67 children with OM were compared with 134 age- and sex-matched controls. While no association was reported for ETS exposure and OM, numbers were not shown.
Etzel *et al.*, 1992	prospective	132 children followed between age 6 months and 3 years with regular ear checks and semiannual serum samples. Children with serum cotinine concentrations greater than 2.5 ng/mL had a 38% excess of new-onset otitis media with effusion compared with unexposed children (incidence density ratio = 1.38; 95% CI = 1.21, 1.56). Peak risk occurred before 24 months of age.

TABLE 6.4
STUDIES OF MIDDLE EAR EFFUSION (MEE) OR OTITIS MEDIA (OM) VS. ETS EXPOSURE NOT REVIEWED BY THE SURGEON GENERAL (1986), NRC (1986), OR U.S. EPA (1993)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Kallail (1987)	case-control	119 school children with hearing loss on audiometry were compared with age- and sex- matched classmates. There was a nonsignificant excess of ETS exposure among the children with hearing problems who were later confirmed by physicians to have "middle ear problems."
Hinton (1988)	case-control	70 children aged 1-11 years referred to ENT clinic (n=26) or optometry clinic (n=44) were screened; 100% of the former and 41% of the latter had MEE. Comparison of children with and without MEE revealed a nonsignificant excess of cases from smoking homes.
Zielhuis (1989)	case-control (nested in prospective)	1,439 preschoolers were followed from age two to four with tympanometry at 3-month prospective) intervals. Incident cases of OM with MEE were compared with controls from same cohort. A nonsignificant excess of smoking was apparent among the parents of cases (OR = 1.11; p = 0.643).
Barr (1991)	case-control	115 children aged 1.5-11.5 years who were referred for ear surgery were compared with surgical patients with nonotologic diagnoses. No difference in self-reported parental smoking habits was observed.
Green (1991)	case-control	164 children aged 1.5-8 years who were seen in ENT clinic for ear pain and hearing loss were compared with like number of nonotologic outpatients. OR for ENT clinic attendance and self-reported maternal smoking = 1.92 (95% CI = 1.23 - 2.99).

TABLE 6.4 (continued)
STUDIES OF MIDDLE EAR EFFUSION (MEE) OR OTITIS MEDIA (OM) VS. ETS EXPOSURE NOT REVIEWED BY THE SURGEON GENERAL (1986), NRC (1986), OR U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Pönka (1991)	prospective	2,216 children in day-care centers were followed for average of one year with interview determination of any medical causes of absence, as well as home ETS exposure. "No significant relationship" between historically reported OM episodes and ETS exposure (numbers not given).
Ra (1992)	cross-sectional	87 10-month-old infants tested for hearing loss. ETS exposure at home was associated with a 4.9-fold increase in hearing loss (49% prevalence in ETS-exposed children vs. 10% prevalence in nonexposed, $p = 0.001$).
Collet (1995)	cohort	918 pre-school children followed from birth to age four. ETS exposure determined prospectively. History of OM determined by parental questionnaire at age four. Maternal smoking of ≥20 cigarettes/day associated with increased risk of recurrent OM (defined as ≥ 4 occurrences) RR = 1.8 (CI = 1.1 - 3.0), but not with single episodes RR = 0.9 (CI = 0.6 - 1.4). Trend of increasing risk of recurrent OM with increasing number of cigarettes smoked. No effect of paternal smoking.
Ey (1995)	cohort	1,013 children followed during first year of life. ETS exposure determined by questionnaire at birth and at one year. Episodes of OM determined by review of medical records. Maternal smoking of ≥20 cigarettes/day associated with increased risk of recurrent OM (defined as ≥ 3 episodes in 6 months or ≥ 4 episodes in a year): OR = 1.78 (95% CI = 1.01 - 3.11), but not with single epsodes OR = 1.29 (95% CI = 0.74 - 2.24). Low birth weight (<3.5 kg) and heavy maternal smoking associated with three-fold increased risk of recurrent OM (OR = 3.29, 95% CI = 1.71 - 6.36). No effect of paternal smoking.

TABLE 6.4 (continued)
STUDIES OF MIDDLE EAR EFFUSION (MEE) OR OTITIS MEDIA (OM) VS. ETS EXPOSURE NOT REVIEWED BY THE SURGEON GENERAL (1986), NRC (1986), OR U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Kitchens (1995)	case-control	History of ETS exposure of 175 children (cases), aged three or younger, with MEE, recurrent OM or adhesive OM requiring tympanostomy tubes compared with 175 age-matched controls. Cases significantly more likely than controls to have household exposure to ETS (OR = 1.66, p = 0.049). ORs related to smoking status of primary or secondary caretakers (typically the mother and father, respectively) alone were also elevated, but nonsignificant. Within case group there was no difference in outcome between those exposed and those not exposed to ETS when followed prospectively.

Overall, the epidemiologic data strongly support a relationship between ETS exposure in the home and either acute otitis media with effusion or serous otitis media (middle ear effusion without acute infection), particularly among children under two years of age. Limitations of available data on the chronicity of physical findings, as well as the differing patterns of recruitment in the various studies, make it impossible to distinguish separate relationships between ETS exposure and acute serous otitis media, chronic serous otitis media, and acute infectious otitis media.

Several reports on the relationship between ETS exposure and otitis media have been published since the draft release of the earlier draft of this chapter (Collet *et al.*, 1995; Ey *et al.*, 1995; Kitchens *et al.*, 1995). The results of these investigations (summarized in Table 6.4) are consistent with the conclusions articulated above.

6.1.3.4 Biological Plausibility

Eustachian tube dysfunction (ETD) plays a central role in the pathogenesis of middle ear disease. While the U.S. EPA did not find plausible biological mechanisms for ETS-related acute otitis media, there are at least four mechanisms whereby ETS might produce Eustachian tube dysfunction. These include:

1) Decreased mucociliary clearance

   At least in active smokers, cigarette smoke is well known to interfere with normal ciliary activity in the tracheobronchial tree (Wanner, 1977). Intact ciliary function is important for the proper barrier function of the Eustachian tube against the entrance of microorganisms (Sismanis, 1991). To our knowledge, however, there is no direct experimental evidence regarding the effects of ETS on ciliary function in the Eustachian tube at this time.

2) Decreased Eustachian tube patency due to adenoidal hyperplasia

   Said (1978) documented an increased prevalence of ETS exposure among children previously referred for tonsillectomy and/or adenoidectomy, and Corbo (1989) found a similar association among children with a history of tonsillectomy and adenoidectomy, rhinitis, or snoring. While many variables may govern whether a given individual has surgery, the common denominator among these conditions is lymphoid hyperplasia and decreased upper airway patency. Adenoidal hyperplasia is a recognized risk factor for the development of otitis media (Sismanis, 1991).

3) Decreased patency due to ETS-induced mucosal swelling

   Chronic pathologic changes associated with otitis media with effusion include goblet cell hyperplasia and hypertrophy within the Eustachian tube (Sando, 1991). While direct evidence of ETS-induced goblet cell pathology in the Eustachian tube has not been reported to date in the literature, similar goblet cell hypertrophy has been observed in the lower airways of smokers (Richardson, 1988). Acute upper respiratory tract mucous membrane swelling due to ETS exposure is explored in some detail in Section 6.1.4 (sensory irritation).

4) Decreased patency and impaired mucociliary clearance secondary to increased frequency of viral upper respiratory tract infections (URI's)

   An increased frequency of upper respiratory tract infection in ETS-exposed children was demonstrated by Fleming (1987), and may accompany some of the lower respiratory tract illnesses documented in Section 6.1.2. Viruses are known to immobilize respiratory tract cilia and to produce vascular, secretory, and interstitial changes that compromise airway patency. URI's frequently precede development of otitis media, and experimental induction of rhinovirus infection (the "common cold") decreases upper airway patency and induces Eustachian tube dysfunction (McBride *et al.*, 1989).

6.1.3.5 Dose-response and attributable risk considerations

Etzel *et al.* (1992) estimated that, with the relative risk of otitis media with effusion (OME) as a function of ETS exposure peaking at 1.62 at age 18 months -- and with an estimated exposure prevalence of 38% (North Carolina) -- some 8% of otitis media episodes occurring between ages 6 and 24 months are attributable to ETS exposure. Iverson (1985) calculated that for Danish children attending day care (estimated ETS exposure prevalence, 60%), 15% of middle ear effusions (MEE) may be smoking-related, with the ETS-attributable fraction actually greater in the 6 to 7 year old group than in younger children. Strachan (1989) computed the odds ratio for MEE in 6.5 to 7.5-year-old children as a function of a doubling of salivary cotinine as 1.14 (crude) or 1.13 (adjusted for gender and housing type). As median cotinine levels in that study varied by a factor of 25 (or 4.5 doublings) between the unexposed children and those living with at least two smokers, odds ratios as high as 1.69 were observed in the more highly-exposed children.

An estimate of yearly physician office visits for early childhood otitis media episodes attributable to ETS exposure in California can be derived as follows:

1) According to an activity study sponsored by the California Air Resources Board, 38% of children under age 12 years, statewide, are exposed to ETS at some time during a typical day, with an average exposure time of 202 minutes (Wiley *et al.*, 1991). Broken down by age and sex, 38% of boys and 28% of girls under age three years are exposed to ETS, yielding a pooled exposure prevalence of 33% in this age group.

2) Etzel *et al.* (1992) applied observed incidence densities among ETS- vs. non-ETS-exposed children and an estimated exposure prevalence rate of 38% to obtain an ETS-attributable fraction of 8.2% for OM cases among children between ages 6 months and 2 years in North Carolina. We repeated these calculations using Etzel's data for children ≤ 3 years, applying California's estimated ETS exposure prevalence (p) of 33% for this age group. These figures yielded an ETS-attributable otitis media fraction of 11.2% for California children under age three years. Using the equation below, a standard approach to calculating attributable risk (Lillienfeld and Lillienfeld, 1980) where R is an estimate of the relative risk, we obtained an ETS-attributable risk fraction (a) of 11.1%, with a 95% confidence interval of 6.5 - 15.6%.

$$a = p\,(R-1) / (p(R-1) +1)$$

3) Data from the National Ambulatory Medical Care Survey (NAMCS) indicates that otitis media is the most common outpatient pediatric diagnosis nationwide (accounting for

approximately 18% of all office visits for children under age 5 years). As of the most recent survey, OM was cited as the principal diagnosis for 102 office visits per 100 children (under two years of age) per year in 1990; and for 48 office visits per 100 children aged 2-5 years (Schappert, 1992).

4) In 1990, California had a population of 1,452,250 children under age three years (US Department of Commerce, 1992). Of these children, 424,303 were under age one year, 524,558 were 1-2 years, and 503,389 were in their third year of life.

5) Assuming that ETS-related otitis media episodes generate the same number of total (initial + follow-up) visits as do non-ETS related episodes, one can combine Etzel's data (pertaining to incident cases of otitis media) and the NAMCS data (pertaining to OM-related office visits--both initial and follow-up). (This may be an underestimate, since ETS usually constitutes an ongoing insult to normal Eustachian tube function, in contrast to such events as viral upper respiratory tract infections).

Combining the above data, one obtains an estimate of almost 135,000 (95% confidence limits, 78,615-188,676) office visits per year among California children under age three years for ETS-attributable otitis media episodes:

	Population at Risk	×	Age-specific Otitis Media Visit Rate	=	OM-Related Office Visits	×	ETS-Attributable Fraction	=	ETS-Attributable Visits/Year
Age ≤2 yr.	948,861	×	102/100	=	967,838				
Age 2-3 yr.	503,389	×	48/100	=	241,627				
					1,209,465	×	0.111	=	134,251 (95% CI: 78,615-188,676)

At the national level, this would roughly correspond to 700,000 to 1.6 million physician office visits annually, assuming approximately 88% of U.S. children under age three reside outside California.

6.1.4 Sensory Irritation and Annoyance

A substantial body of literature addresses the acute and reversible irritative effects of ETS on the upper respiratory tract. Symptoms subsumed in this category include eye, throat, and nasal irritation, rhinorrhea, nasal congestion, hoarseness, and odor "annoyance." ETS-related irritant and annoyance effects were reviewed in both the Surgeon General's and NRC reports (U.S. DHHS, 1986; NRC, 1986), and more recently by Samet *et al.* (1991). In the period since these reports were written, additional insight has been gained into the pathophysiology of upper airway irritant responses, and progress has been made in developing objective methods to validate ETS-related symptom complaints. In this section we will first review exposure dynamics and pathophysiology before considering the newer epidemiological and experimental literature.

Whereas ETS is frequently dealt with as a general cofactor in the study of indoor air quality, this literature review has been restricted to studies in which ETS effects are examined directly.

6.1.4.1 Exposure Dynamics

As noted in the chapter on *Exposure Measurements and Prevalence*, ETS consists of a complex and dynamic mixture of particulate and vapor phase constituents. There is some evidence that the perceived odor and irritation associated with ETS derives from the vapor, rather than particulate phase; however, the data are not conclusive (Hugod, 1984; Weber, 1984). The chemical constituents of ETS thought responsible for sensory irritation include aldehydes (formaldehyde and acrolein), ammonia, pyridine, toluene, sulfur dioxide, and nitrogen oxides, among others (U.S. DHHS, 1986; Ayer and Yeager, 1982; Triebig and Zober, 1984).

The site of action of various respiratory tract irritants is thought to be governed by three factors: 1) particle size (for irritants adsorbed to particulates), 2) water solubility (for gaseous and vapor-phase inorganics), and 3) lipid solubility (for vapor-phase organics). In general, the larger the particle or the more water soluble the compound, the higher the proportion of the inhaled dose that is likely to be deposited in the upper respiratory tract, particularly during nasal breathing. In addition, for a given deposited dose of an organic compound, higher lipid solubility augments the irritant efficiency of the stimulus, apparently by increasing access to the membrane receptor (Nielsen, 1991). Of note, many of the gaseous and vapor phase irritants in ETS have sufficient water solubility to be active on the upper respiratory tract (*i.e.*, nasal cavity, nasopharynx, and hypopharynx) (U.S. DHHS, 1986).

6.1.4.2 Pathophysiology

ETS stimulates the sensory apparatus of the upper respiratory tract through four structures: the olfactory, trigeminal, glossopharyngeal, and vagus nerves (cranial nerves I, V, IX, and X). The olfactory nerve is responsible for the sense of smell, and projects to areas of the primitive forebrain responsible for emotional arousal, including the amygdala and portions of the frontal and temporal lobes. The nasal and oral cavities are innervated by the trigeminal nerve, the nasopharynx by the glossopharyngeal, and the oro- and hypopharynx by the vagus; these nerves project to various areas of the brainstem. The trigeminal, glossopharyngeal, and vagus nerves are responsible for the perception of touch, temperature, and sensory irritation (or what has been termed the "common chemical sense") in all head and neck mucosae. The two nasal senses -- olfaction and irritant chemoreception -- as well as the related sense of taste, functionally interact to produce an integrated impression of one's chemical environment (Cain, 1974; Cain and Murphy, 1980; Frank and Rabin, 1989).

The olfactory epithelium occupies a total area of approximately 5 cm^2 bilaterally in the upper reaches of the nasal cavity. The olfactory apparatus is variably stimulated during normal relaxed nasal breathing; "sniffing," or attentive smelling, creates eddy currents which facilitate the delivery of odorant molecules to the olfactory epithelium. Lipophilic molecules diffuse through the nasal mucus layer, probably aided by an olfactory binding protein, to make contact with receptor sites on olfactory receptor cells (Pevsner, 1988). The olfactory receptor cells are the only central nervous system neurons known to regenerate on a regular basis; this may constitute a functional

response to the fact that olfactory receptor cells are directly exposed to a variety of environmental insults (Frank and Rabin, 1989).

In contrast to the limited distribution of olfactory receptor cells, trigeminal nerve endings are located throughout the nasal and oral cavities. (The vagus nerve innervates the lower respiratory tract, including the trachea, and tracheobronchial tree.) Trigeminal fibers carry sensory information of a variety of types; of primary interest here is the chemosensory function of irritant perception. Irritant perception involves free nerve endings which terminate a short distance below the mucosal surface. The nerve fiber type thought to be responsible for mediating airborne chemical irritation (both in the upper and lower respiratory tract) is the small-diameter, unmyelinated, capsaicin-sensitive C fiber (Lundberg *et al.*, 1988, 1991; Silver, 1992), although A_2 (delta) fibers have also been implicated in some studies (Hummell, 1992).

Important for purposes of understanding the upper airway response to ETS is the fact that trigeminal stimulation can activate both long and short reflex arcs. The long reflex arc involves the trigeminal nerve for the afferent (perceptual) limb and the facial nerve (cranial nerve VII) for the efferent (effector) limb. Exposure to intense irritants anywhere within the nasal or oral cavities produces reflex rhinorrhea and lacrimation via a long reflex arc, autonomic (cholinergic) response. On provocative irritant testing (*e.g.*, after ingestion of horseradish), subjects typically experience subjective nasal stuffiness and rhinorrhea and have acute increases in nasal airway resistance, dilation of vessels within the nasal mucosa, and increased content of plasma and glandular proteins in nasal secretions. This response is mimicked by local instillation of methacholine (an acetylcholine analog), and is blocked by pretreatment with atropine (an acetylcholine antagonist) (Raphael *et al.*, 1991).

For mild to moderately intense irritant stimuli, local reflexes may predominate over the long-arc autonomic response. The so-called "axonal" response is a local reaction in which neuropeptides (vasoactive peptides including substance P, neurokinin A, gastrin-releasing peptide, and calcitonin gene-related peptide) are released from sensory nerves near the mucosal surface. Interestingly, this reflex involves the sensory limb of the nerve only, and is analogous to the so-called "wheal and flare" reaction observed upon mechanical stimulation of the skin. Depending upon the specific peptides involved, these mediators produce some combination of engorgement of blood vessels, transudation of fluid and plasma proteins into tissues, stimulation of secretions, and migration of inflammatory cells (Baraniuk, 1990; Lundberg, 1991; Silver, 1992; Widdicombe, 1990). Apparent cross-species differences in both the distribution of mediators and their physiological effects have posed a challenge to researchers attempting to understand the axonal response in the human airway (Bascom, 1991). Newer studies of airway responses to ETS should be viewed against a background of more traditional methods in irritant toxicology. Animals exposed to highly water soluble upper respiratory tract irritants reveal predictable changes in respiratory pattern, including slowing of respiration, sneezing, coughing, and increased secretions (Alarie, 1973). In humans, the analogous respiratory pattern is an involuntary pause during inspiration or actual breath-holding (Cain, 1987a). Exposure levels necessary to produce these responses, however, are generally high, and researchers in the field of indoor air quality and ETS have searched for more sensitive indices of respiratory tract irritation. As noted below, evidence of true "allergic" upper airway reactions to ETS is quite limited.

6.1.4.3 Specific Health Effects

Eye Irritation

In several questionnaire studies, eye irritation was the most commonly reported mucous membrane symptom among non-smokers exposed to ETS (Bascom, 1991; Basu, 1978; Shephard, 1979; Speer, 1968; White, 1991). The cornea is richly innervated with trigeminal nerve endings that are sensitive to both mechanical and chemical stimuli, and blinking occurs reflexively in response to corneal stimulation. Experimentally, Weber *et al.* (1976, 1984, 1987) and Muramatsu *et al.* (1983) exposed volunteers to progressively increasing concentrations of environmental tobacco smoke; as exposure duration and intensity increased, subjects began to report subjective eye irritation, and blink rate also increased. In another human experimental study, researchers measured precorneal (tear) film breakup time, using fluorescein dye both pre- and post-exposure to ETS. A significant decrease in tear film breakup time occurred after ETS exposure (*i.e.*, the tear film was less stable after ETS exposure) (Basu, 1978). Both blinking and lacrimation act as protective responses to airborne irritants by restoring the protective tear film and diluting any chemical insult. The literature on ETS-induced eye irritation was reviewed in greater detail in the Surgeon General's report (U.S. DHHS, 1986, pp. 234-238).

Nasal Irritation

Bascom (1991) and Willes (1992) identified a subgroup of research subjects who reported a variety of nasal symptoms (congestion, rhinorrhea, sneezing, and postnasal drip) upon prior exposure to ETS. This group comprised approximately one-third of their study population, and were labeled the "historically ETS-sensitive" subgroup in the authors' subsequent provocative testing protocol. Using a climate-controlled exposure chamber, the investigators conducted ETS challenge testing, examining a variety of endpoints. Historically ETS sensitive, but not ETS non-sensitive, subjects showed significant increases in nasal airway resistance (NAR) by rhinomanometry after 15-minute exposures to ETS at levels chosen to simulate a smoking lounge. These changes in objectively measured NAR paralleled the onset of symptoms of nasal stuffiness and rhinorrhea. Although the symptoms described above resemble those of allergic rhinitis, the authors noted that only a small proportion of historically ETS-sensitive subjects have positive skin test reactivity to tobacco-leaf extract (see review of tobacco allergy in Stankus, 1988, pp. 283-285). To investigate the mechanism(s) underlying the responses they observed, Bascom *et al.* (1991) performed nasal lavage pre- and post-ETS exposure. Although allergy-like nasal symptoms were provoked acutely, traditional markers of allergic nasal response (including histamine, various kinins, and albumin) were not found to be increased post-exposure. These findings were taken as evidence that acute nasal responses to ETS may occur via non-allergic, irritative mechanisms (see discussion of vasoactive peptides, above). Despite a lack of evidence for direct allergic mechanisms, individuals who display both subjective and objective ETS sensitivity are more likely than ETS-insensitive subjects to have documented non-tobacco allergies, implying a modulatory effect of allergy upon the irritant chemoreceptive system (Bascom, 1991; Cummings, 1991).

Alteration of Sensory Thresholds

Chronic exposure to cigarette smoke has the ability to change apparent chemosensory sensitivity to airborne odorants and irritants; in at least one case, these observations extend to passive as well

as active smokers. Ahlstrom *et al.* (1987) tested smokers, nonsmokers, and passive smokers for odor acuity to n-butanol and pyridine (the latter being a constituent of tobacco smoke). Both active and passive smokers reported lower perceived odor intensities (*i.e.*, were less sensitive) than nonsmokers. Cometto-Muñiz (1982) and Dunn (1982) examined the endpoint of altered respiration (reflex transitory inspiratory pause) as a measure of nasal irritant sensitivity. Both researchers reported higher irritation thresholds (*i.e.*, lower sensitivity) among smokers versus nonsmokers exposed to a non-odorant stimulus (high-level carbon dioxide); they did not, however, test passive smokers. Kjaergaard (1990; 1992) exposed smokers and nonsmokers to carbon dioxide by mask to determine eye irritation thresholds, and found no appreciable difference in sensitivity between the two groups; again, passive smokers were not tested. No published studies were identified which examined trigeminal irritant thresholds among passive smokers.

A number of mechanisms could explain observed sensory shifts in active and passive smokers. Decreased odor acuity among smoke-exposed individuals could result from increased nasal secretions, which in turn would pose an increased diffusion barrier to odorant molecules. Alternatively, habituation (in effect, ignoring the stimulus) may explain the odor perception findings; Ahlstrom (1987) emphasized the latter possibility because passive smokers did not differ from nonsmokers in the number of "zero intensity" responses given. Shifts in irritant thresholds could result from depletion of neuropeptides in trigeminal sensory fibers; this phenomenon has been documented after high-level treatment with capsaicin (the irritant constituent in hot peppers) (Lundberg, 1983). As noted above, however, reports of altered irritant thresholds due to ETS exposure have not appeared in the literature to date.

Odor "Annoyance"

"Annoyance" is a subjective state of displeasure resulting from a defined environmental stimulus. In the context of ambient (outdoor) air pollution, citizen reactions to unpleasant odors are responsible for the majority of publicly initiated complaints to air quality management districts in California, and may give rise to so-called "nuisance" abatement actions. ETS contains a number of odorant compounds (*e.g.*, pyridine) which are typically described as unpleasant. It is not surprising, then, that even in the absence of eye or other mucous membrane irritation, nonsmoking citizens often complain of annoyance from the odor of ETS in indoor settings. This endpoint has been discussed extensively in the National Research Council report (NRC, 1986, pp. 166-181) and by Samet *et al.* (1991, pp. 152-160). In addition to annoyance, indoor air quality researchers have shown that unpleasant odors detract from the sense of well-being of building occupants and interfere with concentration and productivity (Rotton, 1983).

Cain and co-workers (1983) demonstrated that nonsmokers, on the average, are more likely than smokers to complain of an offensive odor when exposed to a given dilution of smoke-contaminated indoor air. They also showed that when smokers and nonsmokers occupy the same air space, air dilution rates required to render odorant levels acceptable to nonsmokers may be unrealistically high from an engineering standpoint. The practical implication of these findings is that apparently only a strict no-smoking policy, or segregation of smokers into areas with separate, nonrecirculating air supplies, protects nonsmoking building occupants from annoyance and associated effects.

6.1.4.4. Dose-response considerations

Cain *et al.* (1987b), using a climate-controlled exposure chamber, found that 10% of nonsmoking subjects complained of unacceptable air quality (either due to eye irritation or odor annoyance) when ETS raised carbon monoxide (CO) levels by 2 ppm over background, and over 20% expressed dissatisfaction at 5 ppm over background. Muramatsu *et al.* (1983) reported that nearly 30% of experimental subjects had complaints of moderate-to-severe eye irritation with ETS-derived CO levels 2.5 ppm over background. By comparison, CO levels can reach up to 10 ppm over background in smoking-permitted offices (average, 2.5-2.8 ppm), and as high as 29 ppm (average, 4.8-17 ppm) in taverns (Triebig and Zober, 1984). Although most experimental work on sensory annoyance has been performed using CO as an index of ETS exposure, some investigators believe that CO, itself being odorless and non-irritating, is an insensitive and unreliable surrogate measure for irritant and odorant exposure (Chapelle and Parker, 1977).

6.1.4.5. Summary

ETS exposure produces a variety of irritative symptoms involving the upper respiratory tract and eyes; increasingly, these endpoints are able to be objectively documented and quantified. In addition to irritation, odor annoyance from ETS may detract significantly from subjective well-being and productivity among building occupants. Experimental studies conducted by investigators familiar with building ventilation practice suggest that, short of prohibiting indoor smoking, protection of nonsmokers against both sensory irritation and odor annoyance can only be achieved through extreme engineering measures.

6.2 Chronic Health Effects

6.2.1 Asthma (induction)

There is considerable evidence that continuing exposure to cigarette smoke results in the induction of asthma in children. Two large cross-sectional studies involving a total of about 8,000 children and adolescents resulted in odds ratios of approximately two for the presence of asthma with parental smoking (Burchfiel *et al.,* 1986) or maternal smoking (greater than 10 cigarettes a day) (Weitzman *et al.,* 1990). In a longitudinal investigation of asthma incidence among 774 children up to 5 years of age at entry, Martinez *et al.* (1992) reported a relative risk of 2.5 (95% CI = 1.4, 4.6) when maternal smoking exceeded 10 cigarettes/day and the mother had at most a high school education. Another prospective study of 770 school children, however, found no effect of maternal smoking on asthma prevalence at the inception of the study or on incidence during 11 years of follow-up (RR = 1.1, 95% CI = 0.7, 1.7) (Sherman *et al.,* 1990). The U.S. EPA (1992, p. 7-51) reviewed these and other studies and stated that, "The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive."

To investigate the relationship between ETS exposure and childhood asthma more thoroughly, a meta-analysis of studies purporting to examine this issue was undertaken. We conducted a MEDLINE search to identify all epidemiologic studies published between 1975 and 1995 examining ETS exposure as a risk factor for the induction of childhood asthma. Sixty-eight studies were identified as potentially relevant. Studies were selected for inclusion if they met the following four criteria. First, the endpoint studied must represent the development of asthma in

persons ≤ 18 years of age. Because of difficulties related to the diagnosis of asthma, particularly in young children, studies that examined outcomes of "wheezy bronchitis" or "constant wheeze/whistling in chest" were also included and analyzed both separately and jointly with those studies which examined only physician-diagnosed asthma. Second, the exposure studied must represent post-natal household sources of ETS. While studies were not excluded for failure to evaluate separately the effects of post- and pre-natal exposures, they were excluded if they only examined *in utero* exposures to ETS. Third, odds ratios or relative risks must be reported or sufficient data must be presented to allow for calculation of risk ratios and estimates of their standard errors. Lastly, studies must be independent. If more than one study reported on the same cohort of children, then the study that best met the previous three criteria was selected for inclusion.

Thirty-one studies were excluded for failure to meet one or more of the inclusion criteria. We extracted the risk ratios and standard errors from each of the remaining 37 studies, or calculated them using formulae given by Greenland (1987).

We used the random-effects model proposed by DerSimonian and Laird for this analysis (1986). Under the DerSimonian and Laird model, a pooled risk ratio (pooled RR) is calculated as a weighted average of the risk sizes reported by each study. Each study is weighted by a factor equal to the inverse of the variance of the true underlying effect size (estimated by the among-study variance (t^2) added to its own within-study variance (s^2)). Because significant among-study variance was detected, potential sources of heterogeneity by subset analysis and linear meta-regressions were evaluated. Indicator variables were created *a priori* to characterize study design (case-control, cohort or cross-sectional), exposure metric (level and method of measurement), outcome metric (wheeze or asthma), method for identifying cases (parental reporting or medical record extraction), year of publication, age of study participants (preschool, school-age, or all ages), location (North America, Europe or elsewhere), and covariates controlled for in the analysis (*i.e.*, age, sex, socio-economic status, family history of atopy/asthma, reporting of parental respiratory symptoms, early childhood respiratory illness, history of breast-feeding and, in studies involving children older than 10 years of age, the children's own smoking habits). These indicator variables were then used in the subset and meta-regression analyses to explore sources of heterogeneity.

Of the 37 studies included in this analysis, all but three reported a risk ratio (RR) greater than 1.0, albeit many were not statistically significant at $\alpha = 0.05$. The pooled RR for those studies with clinically diagnosed asthma as the outcome was 1.45 (95% CI = 1.28 - 1.65) and did not significantly differ from that of studies examining "wheezy bronchitis" or "chronic wheeze/whistling in chest" (pooled RR = 1.47, 95% CI = 1.34 - 1.61) (See Figures 5.1 and 5.2). Subset analyses revealed several potentially important sources of heterogeneity. Significantly higher pooled estimates of risk were derived from the subset of case-control studies that used population-based controls (pooled RR = 2.43, 95% CI = 1.67 - 3.53) and the subset of studies of preschool children in North America or Europe (pooled RR = 2.00, 95% CI = 1.58 - 2.54). There was little evidence of heterogeneity in either of these groups. Both subsets, however, consisted of relatively few studies. Stratifying the data on other study characteristics yielded pooled RRs ranging from 1.14 to 1.86. The subset analyses substantially reduced the inter-study heterogeneity, but did not eliminate it.

Because substantial heterogeneity persisted even after the subset analyses, we fit linear meta-regressions to evaluate the influence of the study characteristics simultaneously. This multivariate approach identified several additional sources of heterogeneity. Studies of preschool children yielded approximately 50% higher risk ratios than those that included older children. Studies that adjusted for gender also tended to yield significantly higher risk estimates than those that did not. Furthermore, while studies controlling for a family history of atopy did not yield significantly different estimates of risk than those studies that did not, limiting the study population to atopic children or to children with a family history of atopy yielded approximately 60% higher estimates of risk. The overall fit of the model was reasonably good ($p = 0.40$), indicating little evidence of unmodeled heterogeneity.

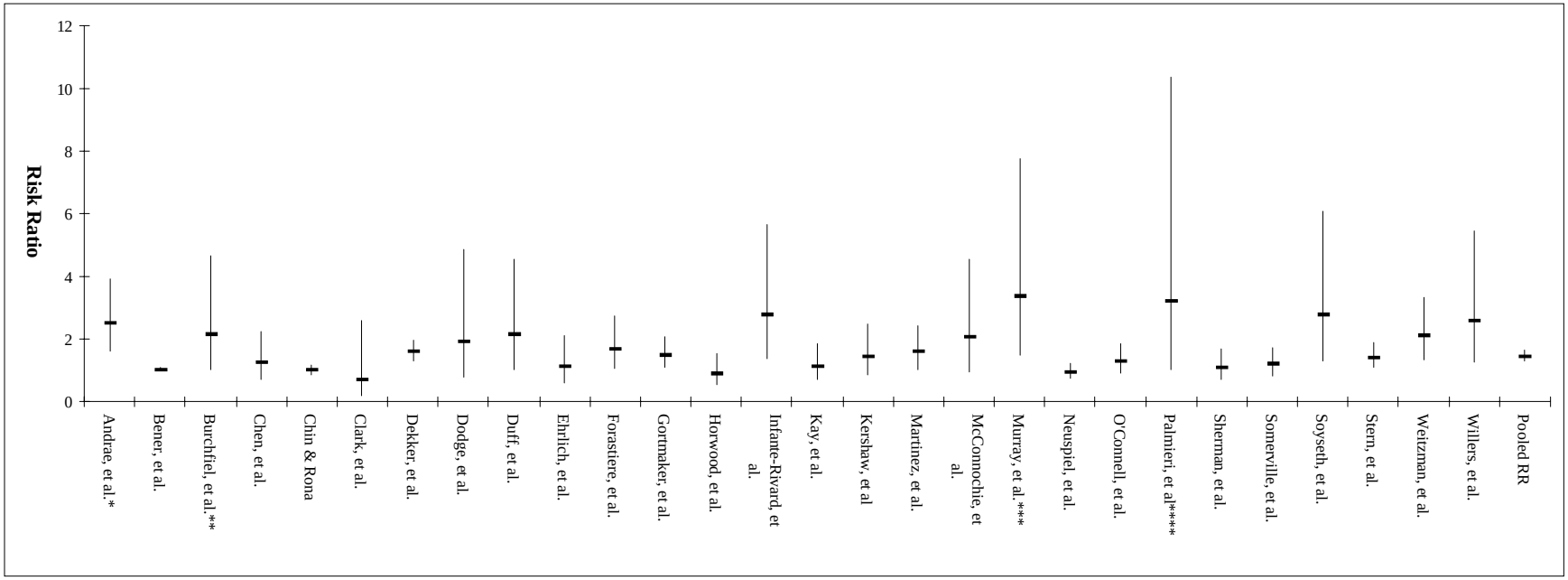
The smoking status of the children being studied was a commonly omitted and potentially important confounder in the studies included in this analysis. To evaluate the influence of this factor on the pooled RRs, the analysis was repeated excluding studies involving children who were 10 years of age or older that did not control for the children's own smoking. This did not change the results, although the confidence intervals became slightly wider (pooled RR = 1.48, 95% CI = 1.28 -1.71).

Most studies relied on crude measures of ETS exposure, *i.e.*, parental reporting of the presence of household smokers or the estimated number of cigarettes smoked in the home. Four studies, however, reported risk ratios in relation to exposures assessed by measurement of salivary or urinary concentrations of cotinine as well as by parental reporting. In all four, the risk ratios associated with exposure to ETS were higher when exposure classification was based on cotinine levels rather than on parental reporting.

The results of this meta-analysis indicate a strong and consistent association between exposure to ETS and development of childhood asthma. This relationship persisted throughout various influence and sensitivity analyses. As anticipated, there was significant heterogeneity of results across studies. Our subset and meta-regression analyses revealed several important sources of heterogeneity related to elements of study design, particularly with respect to exposure assessment.

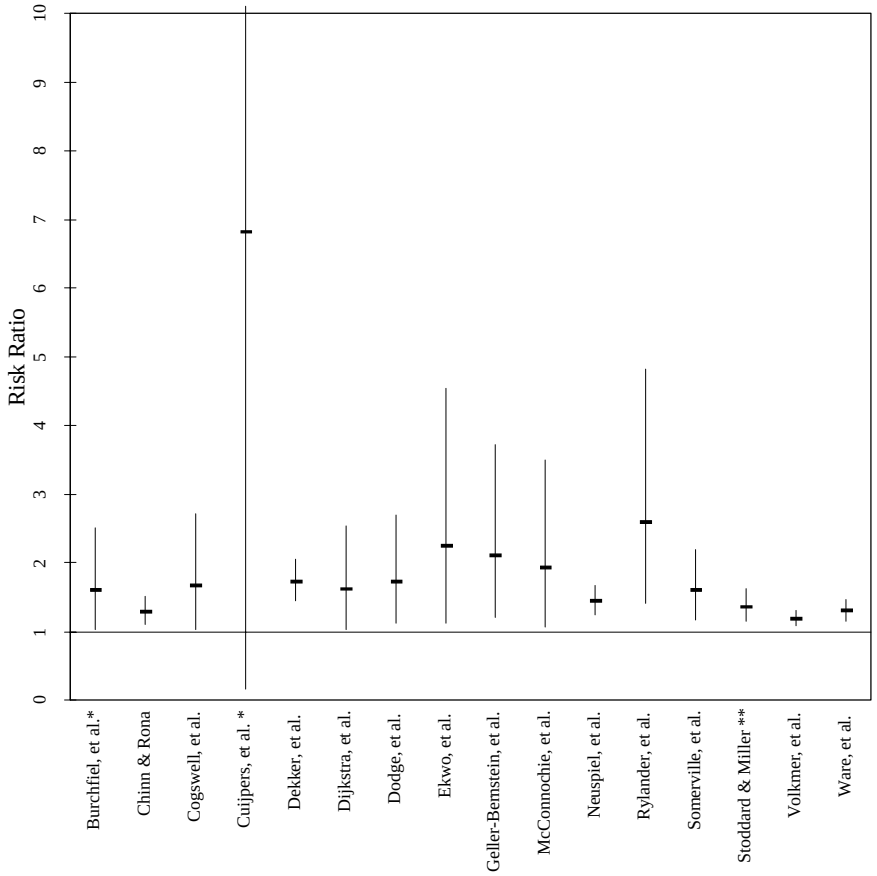
The studies reviewed by U.S. EPA (1992) and those published subsequently indicate that ETS is clearly a risk factor for induction of asthma, particularly in young children. To discriminate between causal and noncausal associations, Hill (1965) listed the following considerations: strength of the association, consistency in results among different studies, the existence of a biological gradient or dose-response, an appropriate temporal sequence between the effect and its putative cause, "coherence" with existing knowledge of the natural history of the disease, and biological plausibility (which is often closely related to, if not indistinguishable from, "coherence"). Other criteria for causal inference listed by Hill (1965) are either obsolete ("specificity") or superfluous in this instance ("analogy" and "experimental evidence"). As noted above, the ensemble of relevant epidemiological studies have found a statistically significant increase in risk associated with parental, particularly maternal, smoking ("strength of association"). The effect estimates tend to be higher in those studies involving pre-school-aged children and in those that used more precise measures of exposure. Nearly all of the point estimates of effect were greater than one; most found effect estimates of similar magnitude despite

FIGURE 6.1
REPORTED RISK RATIOS AND 95% CONFIDENCE INTERVALS
FOR STUDIES THAT USED
CLINICALLY RECOGNIZED ASTHMA AS AN OUTCOME



* In presence of household dampness; ** in boys; *** in children with a history of atopic dermatitis; **** in non-atopic children 3-6 years of age

FIGURE 6.2
REPORTED RISK RATIOS AND 95% CONFIDENCE INTERVALS FOR STUDIES THAT USED "WHEEZING BRONCHITIS" OR "CHRONIC WHEEZING/WHISTLING IN THE CHEST" AS AN OUTCOME



* In girls
** Includes children with physician-diagnosed asthma

the variety of study designs and populations ("consistency"). There appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (*e.g.*, Martinez *et al.* 1992). This finding suggests that a threshold of ETS exposure intensity is required in order to evoke this response. The temporal relation between childhood asthma and parental smoking is not at issue here, since asthma in children is unlikely to precede active smoking by their parents. However, it might be argued that, since the association seems to be strongest between maternal smoking and asthma prevalence in pre-school children, the key exposures may have taken place *in utero*. Several recent studies suggest that pre-natal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994, 1995, Hanrahan *et al.* 1992). It is possible that pre-natal effects may play a role as well in the etiology of childhood asthma. However, the studies by Chen (1986, 1988, 1989), showing effects of paternal smoking alone, as well as studies of ETS exposure linked to increased risks of asthma in nonsmoking adults (Leuenberger *et al.*, 1994), indicate that post-natal exposures can be sufficient to elicit this outcome. Development of asthma as a result of ETS exposure is "coherent" with other investigations demonstrating that both active and passive exposure to cigarette smoke are associated with increases in airway responsiveness, which (as noted above) is a characteristic feature of asthma. The biological plausibility of this relationship is strong: (1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; (2) ETS causes airway hyperresponsiveness; (3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; (4) cigarette smoke causes airway inflammation in active smokers (Niewohner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling.

The U.S. EPA derived a quantitative estimate of risk of asthma induction associated with maternal ETS exposure (U.S. EPA, 1992, pp. 8-10 to 8-13). Using a threshold model, and assuming relative risks ranging from 1.75 to 2.25 for children of mothers smoking more than 10 cigarettes/day, U.S. EPA estimated that 7% to 9% of "all cases of asthma" (presumably pediatric cases only) could be attributable to maternal ETS exposure. This translated to an annual incidence of 8,000 to 26,000 cases attributable to ETS. U.S. EPA also calculated an annual incidence range of 13,000 to 60,000 using a nonthreshold model, noting, however, that a threshold model is more consistent with current epidemiologic data.

There are no California-specific data on asthma prevalence or incidence. Thus, an admittedly simplistic approach to estimating the attributable risk of ETS-induced pediatric asthma in California would be to multiply U.S. EPA's estimates by the percentage of the U.S. population living in this state, *i.e.*, about 12%. This would lead to estimates of 960 to 3,120 new cases of childhood asthma each year using U.S. EPA's threshold model or 1,560 to 7,200 cases using the nonthreshold model.

6.2.2 Chronic Respiratory Symptoms (children)

Dozens of epidemiologic studies have linked chronic domestic ETS exposure with recurrent symptoms of cough, wheeze, and excess phlegm production in children. The NRC report (1986)

concluded, based on a review of nine such studies involving approximately 25,000 subjects, "Children of parents who smoke compared with the children of parents who do not smoke show increased prevalences of respiratory symptoms, usually cough, sputum, and wheezing. The odds ratios from the larger studies, adjusted for the presence of parental symptoms, were 1.2 to 1.8, depending on the symptoms." This range may underestimate the effects of ETS, since adjustment for parental symptoms, which is intended to address possible biased parental reporting of symptoms because of greater somatic awareness, may actually overcorrect for children's symptoms in that it also corrects for parental smoking (Ferris *et al.,* 1985). The Surgeon General's report (1986), reviewing 10 large epidemiologic studies that examined chronic symptoms in approximately 31,500 children, came to a similar conclusion: "[C]hildren whose parents smoke had a 30 to 80 percent excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over six-fold among the studies reviewed. Many studies showed an exposure-related increase in the percentage of children with reported chronic symptoms as the number of parental smokers in the home increased." (p. 48)

The U.S. EPA report (1992) reviewed an additional 14 studies published since 1986, which basically confirmed the findings of the previous major reviews. The U.S. EPA concluded:

> "There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children. The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS... and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4. ... The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0 ..[T]here are significant differences in susceptibility to ETS between individuals. [S]everal factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and being exposed to other environmental pollutants."

The reports by the Surgeon General (U.S. DHHS, 1986), the National Research Council (1986), and the U.S. EPA (1992) concluded that a causal relationship is the most likely explanation of the consistently observed associations between ETS exposure and respiratory symptoms in children. Because this issue has been adequately addressed in these reports, a *de novo* analysis of the primary literature has not been undertaken. More recent published investigations tend to support the conclusions articulated in these reviews. In a study of 343 children, aged 7 - 12, Henderson *et al.* (1995) found odds ratios of 2.9 (95% C.I = 1.2 - 7.0) for ETS exposure in relation to risk of wheeze in nonallergic children and 4.4 (95% C.I = 1.2 - 16.1) in allergic girls but not allergic boys. Goren *et al.* (1995) found significantly increased prevalences of a variety of respiratory symptoms and conditions (cough and sputum, wheeze with and without respiratory infection, bronchitis, and others) associated with maternal or paternal smoking among 8,259 elementary school children in Israel. These and other studies support the conclusion, also stated in the reports by the NRC, the Surgeon General, and the U.S. EPA, that there is sufficient evidence that ETS exposure at home is causally associated with chronic respiratory symptoms (cough, phlegm, or wheezing) in children, particularly infants and young children.

6.2.3 Decreased Lung Development (children)

Numerous cross-sectional and cohort studies have been published since the late 1970s examining the relationship of ETS exposure to various indices of lung function in children. A total of 29 studies, involving lung function measurements on approximately 77,000 subjects, were reviewed by the Surgeon General (1986), the National Research Council (1986), and the U.S. EPA (1992). While the results from all the studies reviewed were not wholly consistent, there was sufficient evidence for these three reviews to reach the conclusion that childhood exposure to ETS affects lung growth and development, as measured by pulmonary function tests (PFTs). Conclusions reported in these reviews are listed below, followed by a description of clinical implications of these findings, plus brief summaries of several more recent studies.

The three major ETS reviews found that:

(1) Some longitudinal (or cohort) studies report a small, but statistically significant, decrease in the rate of lung growth in children (as measured by multiple indices of lung function) exposed to ETS compared with nonexposed children. The magnitude of this decrement in naturally occurring growth, if projected through adolescence, appeared to be three to five percent or less (Surgeon General, NRC, U.S. EPA).

(2) In a majority of cross-sectional studies, ETS-exposed children had modestly lower PFT values, on average, than nonexposed children. These effects were greater in at least some susceptible subgroups (*e.g.*, low birth weight, younger children) or in low SES families (*e.g.*, in which the mothers had less than 12 years of education) (U.S. EPA).

(3) Maternal smoking had a more marked impact on children's PFTs than paternal smoking, though in a data set from China in which all the mothers were nonsmokers, there was an effect of paternal smoking, as well (Chen *et al.*, 1986) (Surgeon General, NRC).

(4) In several studies, lower PFT values tended to be found with an increasing number of smokers in the child's household. In other words, in these investigations there appeared to be an exposure-response relationship (Surgeon General, NRC).

How ETS causes lung function decrements in otherwise healthy children is not known, but the observed effects may be related (at least in young children) to increased susceptibility to respiratory infection or to delayed developmental effects attributable to *in utero* exposure to maternal smoking. Several recent papers suggest that *in utero* or early childhood exposures to ETS may result in changes in lung development that may persist through childhood and adolescence (Cunningham *et al.* 1994, 1995; Hanrahan 1992; Brown 1995). The short-term clinical consequences of these apparent reductions in children's PFTs are likely to be of less importance, however, than their potential long-term implications. As was observed in the Surgeon General's report (U.S. DHHS, 1986), "The absolute magnitude of the difference in lung function is small on average. A small reduction of function, on the order of 1 to 5 percent of predicted value, would not be expected to have functional consequences." Nonetheless, reductions of lung function in childhood may persist into adulthood and increase the risk of developing chronic obstructive pulmonary disease (U.S. DHHS, 1986; NRC, 1986, U.S. EPA,

1992).The likelihood of such potential long-term consequences, however, has not yet been fully evaluated.

Several investigations of the relationship between childhood ETS exposure and lung function have been published since the U.S. EPA reviewed the data on this topic. As with previous studies, the evidence from these investigations is somewhat heterogeneous. The results from several large cross-sectional studies, in particular, tend to support the existence of a relationship between household ETS exposure and decreased lung function. Lebowitz *et al.* (1992) reported an analysis of ETS exposure on PFTs measured at least three times over a 13-year period in 138 Caucasian children (67 boys and 71 girls), aged 5 through 15 upon entrance into the study. ETS exposure was assessed by parental survey: there was no distinction made between light and heavy smoking. The analysis was stratified by gender and by level of lung function (normal or low) at the initiation of the study. This group of investigators had previously reported that, in comparison with children with normal lung function, children with lower initial PFTs experienced their peak lung growth at an earlier age and at a lower absolute value. In this report, there was no ETS effect detected in females who started with either normal or low lung function. Similarly, no effect was detected in males starting with normal lung function. In contrast, boys starting with low lung function who were ETS-exposed had a decreased FEV_1 (forced expiratory volume in one second) between ages 13 and 16, relative to unexposed boys with low initial lung function. Interestingly, growth of the forced vital capacity (FVC, which is a rough indicator of lung volume), in the ETS-exposed boys exceeded that in the nonexposed group between the ages of 17.5 and 23.5. Within this age interval the ratio of FEV_1/FVC (and another similar index of airway obstruction) decreased significantly in the exposed versus the unexposed low-function subjects (and versus the subjects with normal initial lung function). The clinical implications of these findings are unclear, since the apparent accelerated decline in the lung function ratios is at least partly attributable to the increase in the denominator (FVC). Furthermore, though there were a total of 142 lung function measurements made over the course of this study in the low-function males, there were only 28 in this group, including both smokers and nonsmokers. Thus, though it appears that the low-function ETS-exposed males began adult life with an accelerated decline from a lower-than-normal baseline, this type of analysis should be replicated with a larger sample size.

Sherrill *et al.* (1992) recently reported results from a longitudinal study of lung function in a cohort of 634 children (327 males, 307 females) in New Zealand. The children were part of a larger birth cohort whose health status was assessed by questionnaire every two years from 3 to 15 years of age. Questions regarding parental smoking were asked only at ages 7, 9, and 11. Spirometric measurements were performed at ages 9, 11, 13, and 15. There were no statistically significant ETS-related effects on FEV_1 or FVC in males, though females whose parents both smoked tended to have a slower rate of growth in FEV_1 and those exposed to maternal smoking tended to have a lower FVC than the nonexposed ($p < 0.1$ for both findings). The investigators indicated that because of a potential disjunction between somatic growth and lung function growth in adolescence, the ratio of FEV_1 to FVC might be a more accurate measure of lung function growth than either index alone. Using the FEV_1/FVC ratio, detrimental effects of ETS were identified; males, but not females, showed a nonprogressive decrease related to parental smoking. Moreover, in children with asthma or a history of wheezing, progressive decrements in FEV_1/FVC were observed in children of both sexes, compared with an <u>increase</u> in this ratio

observed in nonexposed children with wheeze. The average reduction in FEV_1/FVC by age 15 was 3.9% in ETS-exposed boys with wheeze and 2.3% in girls. As noted by the authors of this report, there does appear to be an ETS-related effect on the subgroup of children with a history of wheezing, but the lack of an obvious separate effect on FEV_1 or FVC weakens this conclusion somewhat.

Wang and colleagues (1994) investigated the relationship between several measures of childhood ETS exposure and annual lung function measurements made in 8,706 nonsmoking white children between the ages of 6 and 18 who were participants in the Harvard Six Cities Study. ETS exposure metrics included: pre-school exposures (during the first 5 years of life), cumulative exposure from age six to the year before each annual examination, and current maternal and paternal smoking as reported each year. In this report, the investigators used regression splines to model pulmonary function growth as a function of ETS exposure, adjusting for age, height, city of residence, and parental education (a surrogate for socioeconomic status). Both current maternal smoking and pre-school exposure to maternal smoking were significant predictors of the children's pulmonary function: there were no significant differences of effect observed in boys versus girls. Both of these measures were associated with small, but statistically significant reductions in FEV_1/FVC and $FEF_{25-75\%}$ (an indicator of flow rates in the smaller airways) through adolescence. Interestingly, early maternal smoking was also associated with a small increase in FVC, which was statistically significant only in children aged 11 to 18. In children aged 6 to 10, current maternal smoking was related to slower growth rates of both FVC and FEV_1, and in older children, with a reduction in the growth rate of $FEF_{25-75\%}$. The findings of an increased FVC and reduced FEV_1 and $FEF_{25-75\%}$ is similar to the report of Lebowitz *et al.* (1992), and suggests that early childhood ETS exposure may induce an exaggerated disjunction in growth rates for airways (as measured by FEV_1 and $FEF_{25-75\%}$) and lung parenchyma (lung volume as indicated by FVC), a process referred to as "dysanapsis". Moreover, after controlling statistically for current ETS exposure, this report suggests that early childhood exposures appear to exert long-lasting effects on lung maturation, as measured by pulmonary function tests.

Rona and Chinn (1993) studied lung function in relation to reported home ETS exposure in 2,756 children, aged 6 1/2 to 12, who took part in a cross-sectional national health survey in 1987 and 1988 in Great Britain. ETS exposure was assessed by parental questionnaire. A large number of potentially confounding variables were controlled for in the analysis, including age, height, ethnic group, weight, birth weight, percentage body fat (as measured by triceps skinfold thickness), reported parental heights, mother's age at child's birth, family size, father's social class, "overcrowding", whether the child resided with one or both parents, mother's educational level, father's employment status, type of cooking fuel, study area, type of school meals, and a variety of the child's respiratory symptoms. The investigators found significant associations of maternal smoking with reduced $FEF_{25-75\%}$ and $FEF_{75-85\%}$ in boys, but not girls. They also found similar gender-associated reductions of FEV_1 with maternal ETS exposure and of $FEF_{25-75\%}$ with total parental smoking, which were of borderline statistical significance. The results of this study are consistent with numerous others in showing an association between reduced childhood lung function and maternal but not paternal smoking. However, the differential effects on boys versus girls remains unexplained and, as the investigators noted, "illustrate the difficulties in making generalizations about the association between lung function and passive smoking in childhood."

Haby and colleagues (1994) assessed the relationship of several variables to spirometric indices (FVC, FEV_1, PEFR, and $FEF_{25-75\%}$) in a cross-sectional study of Australian children in grades 3 to 5 (ages 7 - 12). ETS exposure was assessed by parental questionnaire, and was included as a continuous variable in stepwise multiple regression analyses of predictors of lung function in a group of 2,765 children. Other variables entered in the final models included height, weight, age, gender, current and past asthma, and the presence of a respiratory infection. The investigators reported a linear, dose-related reduction in FEV_1, PEFR, $FEF_{25-75\%}$, but not FVC, where dose referred to the number of cigarettes smoked daily in the home. The magnitude of the reduction was small: a 10-year-old child would be expected to have a 2.4% reduction of $FEF_{25-75\%}$ if more than one pack of cigarettes were smoked in the home every day. The investigators did not report effects of prenatal or early childhood exposure to ETS, whether there were gender differences in the relationship of ETS exposure to spirometry, or the effects of maternal versus paternal smoking. As in several studies described above, Haby *et al.* speculated that the differential effects of ETS on FVC versus the flow-related measures of lung function may be due to dysanaptic growth of the lung.

Cook *et al.* (1993) examined the relationships between several lung function measures and ETS exposure in a population-based sample of 5.0 to 7.9-year old children randomly selected from elementary schools in 10 towns in England and Wales. ETS assessment was conducted by both parental questionnaire and by measurement of salivary cotinine obtained from the participants. Multiple regression models relating the spirometric indices to salivary cotinine were based on data from 2,511 children who had provided complete, acceptable data. The analysis relating lung function to questionnaire-based ETS assessment contained data from 2,500 children. In analyses adjusted for age, gender, height, body mass index, lung function technician, and the town of residence, every lung function index (FVC, FEV_1, FEF_{25}, FEF_{50}, FEF_{75}, and FEV_1/FVC) was negatively associated with salivary cotinine, and all but the FEV_1/FVC ratio were highly significant statistically. Additional adjustment for birth weight, presence or absence of a gas-burning stove, and the head of household's social class (an indicator of SES) did not materially change the estimates. FEV_1 declined linearly with increasing salivary cotinine. The results from the questionnaire-based ETS exposure assessment were more ambiguous, reflecting the increased uncertainty and measurement error associated with such data. Though there was no clear exposure-response relationship between FEV_1 and the numbers of cigarettes reportedly smoked by the mother or the father, when ETS exposure was categorized by the number of smokers to which the child was exposed on a regular basis, all of the above indices except FVC declined with increasing numbers of smokers, though this negative association was significant only for FEF_{25}, FEF_{50}, FEF_{75}, and FEV_1/FVC. As was true of the cotinine analysis, the strongest association was with FEF_{50}. For a small subset of the children (n = 111), salivary cotinine was sampled twice (six months apart): though the mean levels were slightly different (1.59 vs 1.37 ng/ml), this difference was not significant, indicating the stability of ongoing exposure patterns. The cotinine-based analysis supports the existence of an exposure-response relationship between ETS and childhood lung function; however, these investigators could not distinguish between the effects of current versus early childhood exposures.

Two recent reports by Cunningham and colleagues (1994 and 1995) suggest that prenatal or very early post-natal exposures to tobacco smoke components may affect lung development, inducing persistent effects that may be detected throughout childhood. As part of the Harvard 24-Cities

Study, Cunningham *et al.* presented results of an analysis of 8,863 nonsmoking white children, aged 8 -12, in which they examined the relationships of a variety of lung function measures to maternal smoking during pregnancy as well as to current maternal smoking. In regression models adjusted for sex, height, weight, age, parental education, city of residence, and interaction between sex and height, the investigators found decrements in $FEV_{0.75}$, FEV_1, FEV_1/FVC, PEFR, $FEF_{25-75\%}$, and $FEF_{65-75\%}$ that were highly significantly related to both maternal smoking during pregnancy and to maternal ETS exposure in the year preceding the examination. However, when adjusted for current maternal smoking, the associations of these measures with maternal smoking during pregnancy were slightly reduced, but remained highly significant statistically. In contrast, when adjusted for maternal smoking during pregnancy, the effects of current smoking on the children's lung function were markedly decreased and were no longer significant. Boys showed greater ETS-related deficits in all these measures of lung function than girls, but this was due to the greater effects in boys with a history of allergy, asthma, parental asthma, or severe respiratory illness. Among boys and girls with none of these risk factors for decreased lung function, the estimates of ETS-related effects were of similar magnitude. In general, mothers who smoked during pregnancy are likely to continue to smoke afterwards, so these two measures of ETS tend to be highly correlated. However, because of the large size of this study, the investigators were able to undertake a variety of subgroup analyses that highlighted the importance of *in utero* and possibly very early childhood exposure to maternal ETS. Paternal smoking was not a significant predictor of the participants' lung function.

Cunningham *et al.* (1995) undertook a similar analysis with a sample of 493 white and 383 black children, aged 9 to 11, in Philadelphia. ETS exposure history was obtained through the children's mothers' answers to questionnaires. In the statistical analysis, exposures were modeled as dichotomous variables for maternal smoking and for current smoking, and as a continuous variable for the number of cigarettes smoked per day. Pulmonary function testing was conducted at school. Multiple regression techniques were employed to model several lung function measurements as a function of ETS exposure, adjusting for height, weight, age, area of residence, parental education, mother's primary language, and single-parent family status. Models that included boys and girls, or members of both races, required additional adjustments for gender, race, interaction of gender and height, race and gender, race and height, race and weight, and race and age. In regression models for the whole study population, maternal smoking during pregnancy was associated with statistically significant decrements of –8.1% $FEF_{25-75\%}$ (95% CI = –12.9 to –3.1%) and –2.0 % in FEV_1/FVC (95% CI = –3.0 to – 0.9%), while a decrease in FEV_1 was not significant. No decrease in FVC was observed. Larger deficits were observed in black than in white children, with the greatest decreases detected in African-American boys (–19.6% $FEF_{25-75\%}$ (95% CI = –31.1 to –6.1%), –5.9% in $FEV_1/FVC_{\%}$ (95% CI = –8.7 to –2.9%); FEV_1 = –6.0; (95% CI = –10.4 to –1.4%)). These differences could not be explained by potential confounding by SES, prior respiratory illness, or housing characteristics. Current ETS exposure to ETS was not associated with lung function deficits after adjustment for maternal smoking during pregnancy.

In their ensemble, these studies, especially the cross-sectional investigations, tend to support the conclusions reached in the earlier reviews by the NRC, the Surgeon General, and the U.S. EPA regarding the relationships between ETS exposure and lung function in children. However, as

noted above, the data are not entirely consistent. Some of the differences may be explicable by the crudeness of questionnaire-based exposure assessment, which is likely to result in nondifferential misclassification of exposure and a consequent bias towards the null hypothesis of no relationship. Some inter-study discrepancies may also be attributable to the different age ranges of the study populations, especially since early childhood or *in utero* exposures appear to exert long-lasting effects, which may diminish over time. Finally, although the mean changes observed have generally been of small magnitude and uncertain clinical significance, the potential long-term implications of these lung function decrements warrant additional investigation.

6.2.4 Chronic Pulmonary Disease and Respiratory Symptoms (adults)

Several investigators have examined the question of chronic chest symptoms and/or pulmonary function changes in adults exposed to ETS. It is well established that active smoking leads to increased age-related decrements in pulmonary function. For example, in a large multi-center longitudinal study, the yearly decline in FEV_1 was 30-40% greater in smokers than in nonsmokers (Xu, 1992). Smoking also can lead to chronic obstructive pulmonary disease (COPD). COPD is characterized by mucus hypersecretion/infection (chronic bronchitis) and loss of elastic recoil and alveolar integrity (emphysema), resulting in varying degrees of airway obstruction (particularly during expiration) and sputum production. Mechanisms underlying these changes include cigarette smoke-induced bronchopulmonary inflammation, induction of airway hyperresponsiveness, inhibition of mucociliary clearance (and other antimicrobial defenses), goblet cell hyperplasia, release of proteolytic enzymes from inflammatory cells, and possibly inhibition of antiproteases (Snider, 1989, 1991; Wagner, 1992). This section reviews the epidemiologic evidence bearing on the question of chronic exposure to ETS, lung function, and chronic respiratory symptoms in adults.

The Surgeon General's Office (U.S. DHHS, 1986) and NRC (1986) reviewed five, and the U.S. EPA (1992) an additional six, studies of chronic respiratory symptoms and/or pulmonary function among adults exposed to environmental tobacco smoke in the home or workplace; these are summarized below. Several additional studies were found which were not summarized in any of the above reviews.

White and Froeb (1980) surveyed 2100 middle-aged subjects who enrolled in a physical fitness course sponsored by the University of California, San Diego over a ten-year period. Roughly seven-eighths of the registrants were white collar workers. For both sexes, nonsmokers who reported chronic workplace exposure to ETS had, as a group, significantly lower FEF_{25-75} (forced expiratory flow during the middle half of the forced vital capacity maneuver) and FEF_{75-85} values than did non-ETS exposed nonsmokers; comparable decrements were found in the above parameters among light smokers and smokers who did not inhale. By comparison, persons actively smoking at least one pack-per-day for 20 years or more had decrements in the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), which were not seen in passive smokers or light smokers.

Comstock (1981) analyzed cross-sectional data on 1,724 adult participants in two different studies of respiratory symptoms. Non-significant excesses of subjects with an FEV_1 <80% of predicted or an FEV_1/FVC <70% were observed among males exposed to ETS; no such excesses

were seen among women. Most respiratory tract symptoms were equally prevalent among those exposed and not exposed.

Kauffman (1983 and 1989) analyzed questionnaire and pulmonary function data in two cross-sectional studies that included 3,855 French women (aged 25 to 59 years) and 2,220 American women (aged 25 to 74). For most lower respiratory symptoms, odds ratios comparing passive smokers with nonsmokers were elevated, but not to a statistically significant degree. Among French women over age 40, both FEV_1 and FVC were significantly lower among the passive smokers. In the U.S. sample, there was a significantly elevated rate of self-reported wheezing among passive smokers compared to the unexposed group.

Kentner *et al.* (1984) conducted a cross-sectional study of 1,351 office workers, including both a questionnaire and pulmonary function testing. Smokers, ex-smokers, and passive smokers were compared to lifetime non-smokers. Whereas active and prior smokers had significantly lower age- and sex-standardized ventilatory parameters, no such changes were evident among persons whose sole lifetime exposure was passive smoking.

Brunekreef *et al.* (1985) followed 97 nonsmoking rural Dutch females for approximately 15 years with serial measures of pulmonary function. Analyzed cross-sectionally, those women 40 to 60 years of age at the time of the latest measurement who were passively exposed to cigarette smoke in the home had significantly lower peak expiratory flow (PEF) than did the unexposed group. Among those with passive smoke exposure throughout the period of the study, forced expiratory flow at 75% of total lung volume (FEF_{75}) was also significantly lower. Other lung function parameters, while generally lower among passive smokers, were not significantly so. Analyzed longitudinally, however, there was no significant difference in yearly age-related pulmonary function loss between the two groups.

Svendsen (1987) analyzed data from the Multiple Risk Factor Intervention Trial on 1,245 married men aged 35-57 years who had never smoked, roughly a quarter of whom had wives who smoked. Upon entry into the study, the latter had FEV_1 values, on average, 99 ml (2.8%) lower than those with nonsmoking wives (95% CI, 5-192 ml lower). Separating subjects whose wives smoked less than versus greater than one pack per day did not provide evidence of a dose-response relationship, however. Passive smoking histories were validated with serum thiocyanate levels (no difference observed by spousal smoking) and expired air carbon monoxide (significant trend with increasing spousal smoking).

Kalandidi (1987 and 1990) conducted a case-control study, comparing 103 nonsmoking Greek women aged 40-79 who were admitted to the hospital for an initial diagnosis of COPD with 179 similarly aged nonsmoking visitors (*i.e.*, friends and family of patients). A significant trend was observed in the odds ratio for COPD and spousal smoking as the husband's estimated (during-marriage) total cigarette consumption increased, with the OR equaling 1.3 for fewer than $3x10^5$ cigarettes and 1.8 for greater than $3x10^5$ (*i.e.*, greater than approximately 40 pack-years of spousal cigarette smoking; p=0.01 crude, p=0.03 adjusted). Factors adjusted for in the analysis included age, education, rural vs. urban residence, and employment status.

Euler *et al.* (1988) performed a multivariate logistic regression analysis of questionnaire data from 7,445 nonsmoking Seventh Day Adventists in California. The study, which focused mainly on the effects of air pollution, looked at passive smoking as a covariate. Among other variables, self-reported ETS exposure, both in the workplace and in the home, was significantly related to self-reported symptoms of COPD (*i.e.*, breathlessness, sputum production, and wheezing).

Masi *et al.* (1988) did a cross-sectional analysis of 293 nonsmoking men and women, 15-35 years of age, who had previously been recruited for a study of lung function in adolescence and young adulthood. There was a significant decrement in FEF_{25-75}, FEF_{50}, and residual volume as a function of cumulative lifetime exposure to ETS at home (but not at work) among males only. Females showed a significant trend toward lower carbon monoxide diffusion capacity (D_Lco) with increasing cumulative ETS exposure at work (but not at home). The analysis involved a total of 40 test statistics. Of note, the observation of a significantly lower residual volume (RV) in males exposed to ETS at home runs counter to the hypothesis that ETS exposure produces clinically significant COPD, since an *elevated* RV is normally observed in COPD.

Hole *et al.* (1989) interviewed and examined 671 lifetime nonsmoking Scottish men and women, 243 of whom lived with one or more smokers. Age-, height-, and sex-adjusted FEV_1 values were significantly lower among those exposed to ETS compared to those not exposed (difference = 3.5%). A variety of respiratory symptoms (*e.g.*, shortness of breath, sputum production) were elevated to a nonsignificant degree among the ETS-exposed group.

Schwartz and Zeger (1990) reanalyzed data from a diary study of acute respiratory symptoms among 100 student nurses. Subjects completed daily entries for as long as three years. Variables used in the analysis included smoking and ETS exposure history, allergy status, and various measures of outdoor air quality. Controlling for personal smoking, self-reported phlegm production was significantly more common among students with smoking, as opposed to nonsmoking, roommates (OR = 1.41; $p < 0.001$).

The studies described below were not included in the Surgeon General's, NRC, or U.S. EPA reports.

Schilling *et al.* (1977) conducted a cross-sectional analysis of questionnaire and pulmonary function data from 376 families in Connecticut and South Carolina. They found no significant differences in adult symptom reporting rates or, controlling for prior smoking history, in pulmonary function measures as a function of spousal smoking habit.

Masjedi *et al.* (1990) administered a questionnaire to (and performed pulmonary function tests on) 275 lifetime nonsmoking hospital employees and physicians. Among male subjects (n=167), significantly lower spirometric values (FEV_1, FVC, and FEF_{25-75}) were observed for those who reported ETS exposure at work (not home) versus those who did not. Among females, no systematic differences were found with ETS exposure at either work or home. A potential confounder in the study was the high level of ambient air pollution in the area surrounding the recruiting hospital (Teheran, Iran).

More recently, Jaakkola *et al.* (1995) reported the results of a longitudinal study of lung function in 117 nonsmoking young adults (aged 15 to 35) in Montreal, Canada who were tested in 1981-83 and again in 1988-89. ETS exposures at home and at work during and prior to the study were assessed by questionnaire. In multiple linear regression analyses controlling for age, gender, height, Quetelet index (wt/ht^2), baseline FEV_1, baseline FEF_{25-75}, atopic status, and the presence of wheeze at baseline, these investigators did not find a significant relationship between either current or past home or work exposure to ETS and the change in FEV_1 or in FEF_{25-75} during the study period In a subanalysis of the subjects who were 25 years of age or younger at baseline (n = 62), Jaakkola and colleagues found that work-related ETS exposure during the study period was associated with a slight, but significant increase in the rate of decline of FEV_1. They also calculated 95% confidence intervals on their estimates, indicating that, given the exposure conditions and baseline health of their study population, the changes in lung function during young adulthood potentially attributable to ETS would be approximately −1.0 ml/yr per pack-year, which would be of little clinical importance. It should be noted, however, that 80% of the men (total n = 60) in this study had no ETS exposure at home during the study period, while another 8% were exposed to fewer than 10 cigarettes/day; only one man was exposed to a pack or more on a daily basis. For women (n = 57), the corresponding numbers were 45% with no ETS exposure at home, 33% with exposure to less than half a pack, and six who were exposed to a pack or more. The frequencies of work-related exposures were greater, but still reflected light to moderate exposure at most. Thus, as the investigators acknowledged, their findings would not necessarily be representative of what might occur with more frequent exposure in smaller indoor spaces with poorer ventilation. Also, the authors of this small study focused only on changes during the study period and did not report whether baseline lung function was related to prior ETS exposure.

Dayal and co-workers (1994) undertook a case-control study of the relationship between self-reported, previously diagnosed obstructive lung disease (including asthma, chronic bronchitis, and emphysema), where cases and controls were selected from a probability sample of 4,200 individuals residing in nine Philadelphia neighborhoods in 1985-86. In an analysis restricted to never-smokers, the cases (n = 219) were matched on age, gender, and neighborhood with three randomly selected controls. The matching on neighborhood was intended to control both for SES and local environmental conditions, such as air pollution. In conditional logistic regression analysis that also controlled for type of heating and whether a gas stove was present (and possibly other variables), Dayal *et al.* found a significant relationship between reported obstructive lung disease and household ETS exposure involving one or more packs a day, corresponding to an odds ratio of 1.86 (95% CI = 1.21 - 2.86). While this result suggests that household ETS exposure increases the risk of obstructive lung disease, the interpretation of this study is limited by a lack of information about the study populations (*e.g.*, basic demographics) and about the temporal character of the disease outcomes in relation to the study date -- in other words, whether the disease(s) reported by the participants were “ever-diagnosed” or still present (*i.e.*, asthma and chronic bronchitis).

Xu and Li (1995) analyzed relationships of household and occupational ETS exposure on pulmonary function in 1,033 adults (including 502 never-smokers), aged 40 to 69, in a residential area of Beijing. Current ETS exposure was assessed by questionnaire. In stratified multiple regression analyses controlling for age, income, educational level, personal smoking status, indoor

use of coal stoves for heating or cooking, and occupational exposures to dusts, gases, or fumes, Xu and Li reported reduced levels of FEV_1 and FVC associated with ETS exposure, which were statistically significant in never-smoking men, but not women. While almost all of the estimates of effect of ETS exposure on lung function in ever-smokers were also negative, these were significant only for the pooled group (men and women) exposed both at home and at work. Also, when the exposures were categorized as low (1 - 5 cigarettes/day) versus high (>6/day), Xu and Li found evidence of linear exposure-response relationships, which were statistically significant for FEV_1 and FVC in never-smoking men and for ever-smoking women. In this study, the magnitudes of the lung function decrements reported to be associated with ETS exposure were substantial (4.2 ± 1.8 ml/cigarette smoked in the household for FEV_1 and 5.2 ± 1.9 ml/cigarette for FVC). However, the exposure conditions in Beijing are clearly different from those obtaining in California or the U.S., potentially limiting the generalizability of these findings.

Robbins and co-workers (1993) reported that several measures of childhood and adult ETS exposure were associated with onset of airway obstructive disease (AOD, comprised of asthma, chronic bronchitis, and emphysema) in 3,914 nonsmoking Seventh Day Adventist adults in a prospective investigation. Questionnaires about both symptoms and historical ETS exposure were administered to study participants in California in 1977 and again in 1987. Though all three disease entities constituting AOD were self-reported, the questions about both asthma and emphysema were structured to require a physician's diagnosis. Statistical analysis relied on multiple logistic regression modeling of AOD onset over the 10-year period, controlling for age, education level (an indicator of SES), gender, years of past smoking (15% of the study population), and an indicator of chronic exposure to particulate air pollution. Robbins *et al.* reported that several, but not all, qualitative measures of ETS exposure were associated with an increased relative risk of developing AOD during this interval, including adult plus childhood exposure (RR = 1.72, 95% CI = 1.31 - 2.23), but not childhood or adult exposure alone (RR = 1.09, 95% CI = 0.69 -1.79 and RR = 1.28, 95% CI = 0.90 - 1.79, respectively). Similarly, examining the outcomes of chronic bronchitis and asthma separately, they reported increased RRs for both outcomes in relation to combined adult and childhood ETS exposures: RR = 1.71 (95% CI = 1.27 - 2.27) for chronic bronchitis and RR = 1.89 (95% CI = 1.13 - 3.15) for asthma. Several sensitivity analyses indicated that these findings were robust: specifically, the ETS risk estimates changed little when the analysis was restricted to never-smokers, and when terms were included in these regressions for childhood respiratory illness and frequency of childhood colds. One unexpected finding in this report, however, was that the RR for AOD corresponding to having actively smoked for 10 years was lower (RR = 1.27, 95% CI = 1.10 - 1.47) than those estimated for the combined adult and childhood ETS exposures. The authors explained this unusual result as a combination of factors: the low prevalence of ever-smoking adults in the study population (15%), the long time that had elapsed since the active smokers had quit (mean = 21.4 year), and the "short" period of time during which active smoking had taken place (mean = 14.8 year).

In a separate analysis of virtually the same data set, Greer *et al*. (1993) examined the incidence of new cases of asthma as a function of adult ETS exposure ("years lived with a smoker" and "years worked with a smoker"), controlling for years of active smoking, ozone and particulate air pollution, occupational dust and vapor exposures, childhood history of AOD, age, gender, and education. In the final models that Greer *et al*. reported, the incidence of "definite asthma" by

reported symptoms or reported physician diagnosis during the 10-year interval was significantly related to occupational ETS exposure, with a relative risk of 1.45 (95% CI = 1.21 - 1.80). Separate subanalyses for men and women produced similar results. Greer *et al*. (1993) also obtained medical records for 49 of the self-reported cases of asthma, and validated the diagnosis in 30 (61%), suggesting a reason for caution in interpreting the results of these investigations. Although these investigators indicated that the relative risks for occupational ETS exposure remained significant when only the validated asthma cases were used in the regression models, the magnitudes of the risks were not specified. Based on the results of these two studies, it seems likely that ETS exposure is significantly related to self-reported symptoms of AOD, but the extent to which this relationship holds true for each of the subsets of AOD (*i.e.*, asthma and chronic bronchitis) would require additional research.

In a cross-sectional study of nonsmoking women in Singapore, Ng *et al.* (1993) reported increased risks of chronic respiratory symptoms and reduced FEV_1 associated with household ETS exposure. Symptom and ETS exposure data were collected from 1,438 women, 1,282 of whom were life-long nonsmokers. Of the latter, 1,008 provided acceptable FEV_1 tracings for analysis. In multiple logistic regressions that adjusted for age, race, area and size of residence (indicators of SES), and employment status, (and for chronic rhinitis and eczema, when examining odds ratios for wheeze and physician-diagnosed asthma), Ng and co-workers found elevated odds ratios for all respiratory symptoms where the women were exposed to one or more heavy smokers (defined as those who smoked ≥ 20 cigarettes/day). ORs were significantly elevated for chronic or usual cough (OR = 3.79, 95% CI = 1.76 - 8.14), cough at least 3 months out of the year (OR = 3.01, 95% CI = 1.13 - 8.03), breathlessness on exertion (OR = 1.83, 95% CI = 1.30 - 2.58), and wheeze (OR = 2.69, 95% CI = 1.23 - 5.88). For women exposed to one or more light smokers (*i.e.*, those consuming <20 cigarettes/day), the only significantly increased OR was for usual or chronic cough (OR = 2.84, 95% CI = 1.29 - 6.24). Restricting the analysis to housewives (n = 548), who would be expected to be exposed to ETS only at home, resulted in elevated ORs for all symptoms examined except physician-diagnosed asthma, though these increases were statistically significant only for chronic cough and breathlessness on exertion. Analysis of FEV_1 in relation to ETS, controlling for the same potentially confounding factors and effect modifiers, with the addition of the variable height, indicated that small, but statistically reductions in lung function were associated with the presence of one or more light or heavy smokers in the home, whether the analysis included all women or only housewives. In this study population, frequency of gas cooking was not associated with increased risks of respiratory symptoms (except breathlessness on exertion), but was associated with small reductions in lung function. The investigators' conclusions would have been strengthened had they also controlled for this potential confounder in the ETS analyses.

In a cross-sectional study of 4,197 never-smoking adults, aged 18 to 60, Leuenberger *et al.* (1994) examined the relationships between ETS exposure and a variety of symptoms. Information on both exposure and symptoms were obtained though structured interviews. Analysis involved multiple logistic regression that controlled for age, gender, body mass index (weight/height^2), area of residence, parental and sibling history of asthma, and atopy (determined by a serum immunofluorescence assay for specific IgE against common inhalant allergens). Leuenberger and co-workers found elevated odds ratios for all respiratory symptoms examined

except allergic rhinitis, as follows: wheezing apart from colds (OR = 1.94, 95% CI = 1.39 - 2.70), physician diagnosed asthma (OR = 1.39, 95% CI = 1.04 - 1.86), dyspnea on exertion (OR = 1.45, 95% CI = 1.20 - 1.76), symptoms of bronchitis (OR = 1.59, 95% CI = 1.17 - 2.15), and symptoms of chronic bronchitis (OR = 1.65, 95% CI = 1.28 - 2.16). These estimates of elevated risk did not change significantly when a variety of sensitivity analyses were undertaken, such as excluding subjects whose mothers had ever smoked, excluding subjects who were likely to have been active smokers (determined by measuring the concentration of exhaled carbon monoxide in their breath) and controlling statistically for low educational level (an indicator of SES), and for occupational exposures. Moreover, these investigators found evidence of a dose-related increase in risk for all these symptoms where dose was represented as either reported hours per day or years of passive smoke exposure. This study addressed most concerns usually raised about potential confounders in epidemiological studies of ETS-related health effects, notably differential symptom reporting by those whose mothers smoked during pregnancy or during the subjects' early childhood, by active smokers claiming to be nonsmokers, by factors related to SES, and by occupational exposures. On the basis of the studies reviewed prior to 1987, the Surgeon General's Office (U.S. DHHS, 1986) concluded that "The small magnitude of effect implies that a previously healthy individual would not develop chronic lung disease solely on the basis of involuntary tobacco smoke exposure in adult life." On the basis of more recent studies (particularly Hole *et al.*, 1989 and Svendsen *et al.*, 1987) the U.S. EPA (1992) estimated a 2.5% lower FEV_1 and a 30-60% increase in respiratory symptoms among passive smokers as compared to unexposed individuals. U.S. EPA further concluded that the "...effects of passive smoking on lung function are approximately comparable to those reported for light (<10 cigarettes/day), male active smokers." The report did point out that several of the studies reviewed were problematic with respect to control for potential confounding variables.

Prior to the publication of relevant recent studies, we concurred with the Surgeon General's Office and the U.S. EPA that the effect of chronic ETS exposure upon pulmonary function in otherwise healthy adults is likely to be small in comparison to active smoking, and is unlikely, by itself, to result in clinically significant chronic disease. The results of Leuenberger *et al.* (1994), Robbins *et al.* (1993) and other recent papers, however, suggest that ETS exposure may make a significant contribution to chronic respiratory symptoms in adults. In conjunction with reports of acute lower respiratory tract symptoms among individuals with pre-existing asthma (see Section 6.1.1), the small differences in lung function found in epidemiological studies are a basis for concern and further study.

6.2.5 Studies on Lung Development in Animals

Evidence for effects of mainstream smoke (MS) exposure of pregnant rodents on fetal lung development has been provided over the past ten years. More recently, effects of sidestream smoke (SS) on both prenatal and postnatal lung development, function and airway reactivity have been studied in rats. In animal studies, MS and SS are distinguished by the mode of generating the smoke, but all exposures have been passive or environmental (i.e., smoke has been inhaled from ambient air). SS differs from ETS in that it does not contain exhaled mainstream components.

Studies of lung development were undertaken after data indicated a proportionally greater growth retardation in fetal lung than in other organs as a result of MS exposure of pregnant rats (Bassi *et al.*, 1984). Histopathology and morphometry studies of the growth-retarded lungs demonstrated increased sizes and reduced numbers of primitive alveoli (saccules) leading to a reduced surface area available for gas exchange in the term fetus (Collins *et al.*, 1985). When fifteen-day-old rats were examined after *in utero* smoke exposure, gas diffusion capacity of the lung as determined from histomorphometry was similar to that of controls (Lichtenbeld and Vidic, 1989). Nonetheless, biochemical measures suggested delayed septal growth and development of lung interstitial cells (Vidic *et al.*, 1985). Since septa subdivide existing alveoli to produce new alveoli, these findings are consistent with the lower number of alveoli seen in fetuses at term (Collins *et al.*, 1985). However, functional lung parameters (respiratory capacity, reactivity, immune defense) were not evaluated in these studies.

Developmental studies of lung function and reactivity have recently been undertaken in rats using methodologies specifically designed for producing SS exposure (Teague et al, 1994).

Joad and colleagues (1993; 1995a) studied functional lung parameters (compliance, resistance, reactivity) in adult rats exposed to SS prenatally and/or postnatally. The rats were 7-10 weeks of age (sexual maturation in rats occurs at 5-6 weeks of age) at the time of the lung function tests. As measured in isolated perfused lungs, compliance was decreased 24%, and reactivity (to methacholine challenge) was 200% greater in rats exposed to SS both prenatally and postnatally. Furthermore, the number of neuroendocrine cells, an immature cell type in the lung, was 22-fold greater after the combined gestation/lactation exposure. Hyperplasia and persistence of neuroendocrine cells, which contain mediators of bronchoconstriction, were considered the basis for reduced compliance and increased reactivity. The SS air concentration in this study was 1 mg/m^3, which is at the top of the range of ETS exposures recorded in any environment (U.S. EPA, 1993).

These effects were not seen when exposures occurred only prenatally or only postnatally (Joad *et al.*, 1993). The postnatal exposures were given from day 2 through 7-15 weeks of age, or only at 15 weeks of age, and thus covered the entire period of postnatal lung development. The lack of effect emphasizes the importance of exposure during fetal as well as postnatal stages of lung development. In rats exposed only postnatally to SS, cell division in epithelial cells of terminal but not proximal bronchi was lower than in controls at 7 and 14 days of age. Since cell division is an immature property of the bronchiolar epithelium, this indicated stimulation of lung maturation, as also suggested by studies of enzyme induction.

Induction of metabolic enzymes by SS in the immature lung has been studied in the postnatal period. The establishment of metabolic competence of the lung is delayed well into the postnatal period in laboratory animals as well as in humans. Aryl-hydrocarbon hydroxylase (AHH), also known as cytochrome P450 1A1, was induced in lungs of rat offspring who were exposed to MS constituents *in utero*, by nursing or directly through inhalation after birth (Bilimoria and Ecobichon, 1989). This enzyme is know to be induced by polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke (Bilimoria and Ecobichon, 1980). Little or no induction was seen in hamster or guinea pig offspring. The results seen in rats demonstrate that tobacco smoke components can reach the fetal lung of rats and produce a biochemical response. Other studies

demonstrated that SS exposure can alter the ontogenetic time course of appearance of lung enzymes (Ji *et al.*, 1994). In rat pups exposed to SS from birth at a concentration of one mg/m^3, cytochrome P450 1A1 was seen earlier, and persisted at high levels longer after the normal developmental peak. Clara cells, an epithelial cell type that contains P450, also demonstrated reduced cell proliferation in late maturing areas and increased NADPH reductase expression, two indicators of early maturation. Two other Clara cell enzymes, cytochrome P450 2B and Clara cell secretory protein, were not affected. Premature induction of metabolic pathways could be seen to serve a protective function in the immature lung; however, production of reactive intermediates that induce oxidative damage and genotoxicity is also possible.

Postnatal SS exposure has also been studied in connection with lung responsiveness associated with the C-fiber system. C-fibers in the lung mediate an airway defense response which includes mucus secretion, bronchoconstriction, and coughing in response to irritants. Compliance, resistance and lung morphology were measured in the isolated, perfused lungs of 43-day-old guinea pigs that had been exposed to SS at a concentration of one mg/m^3 from eight days of age (Joad *et al.*, 1995). Baseline compliance was increased modestly (17%) by SS exposure, but lung morphology and baseline resistance were not altered. The response of the lung to capsaicin, a specific C-fiber agonist, was reduced by SS exposure but the response to substance P, which is released by the C-fiber, was not affected; this suggests a down-regulation of C-fiber responsiveness (i.e., the lung is still able to respond to directly to substance P, but doesn't respond to capsaicin, indicating that decreased responsiveness to capsaicin involves the C-fibers). Reduced C-fiber responsiveness indicates a depressed defense response that could result in greater penetration of toxicants and infectious agents into the lung and be responsible for higher incidence of respiratory problems.

6.3 Susceptible Populations

6.3.1 Atopy/Atopic Dermatitis

Atopy refers to an inherited predisposition to develop IgE antibodies against common environmental and dietary allergens. This predisposition is manifested in several chronic conditions: allergic asthma, atopic dermatitis, allergic rhinitis, and allergic gastroenteropathy. Allergy (atopy with or without high serum levels of IgE) can be documented in most cases of asthma (Burrows *et al.*, 1989, as cited in U.S. EPA, 1992), although exercise-induced bronchospasm, reactive airways dysfunction syndrome, and many types of occupational asthma can occur in nonatopic individuals.

The evidence relating ETS exposure to the development of atopy is mixed. Several studies have shown that exposure to passive smoke is significantly associated with total serum IgE concentration and may therefore affect the development of allergic disease. Studies that showed a relationship between active smoking and IgE levels, such as those reviewed in U.S. EPA (1992) (Gerrard *et al.*, 1980; Burrows *et al.*, 1981; Zetterstrom *et al.*, 1981; Taylor *et al.*, 1985), prompted researchers to investigate the relationship of passive smoke exposure and allergic sensitization in children. Several studies have shown up to a 2.2-fold increased risk of atopy in children of smoking mothers (Weiss *et al.*, 1985; Martinez *et al.*, 1988). Ronchetti *et al.* (1990) analyzed the same population used by Martinez *et al.* (1985) and found that total serum IgE levels and eosinophil counts were significantly greater in children of smoking parents.

In contrast, two studies of maternal active and passive smoking during pregnancy showed no association of *in utero* ETS exposure and umbilical cord blood IgE (Oryszczyn *et al.*, 1991; Ownby *et al.,* 1991). High levels of cord blood IgE are predictive of the development of childhood allergy. A group of 99 singleton births in a hospital in Paris, France were used to validate use of cord blood cotinine and maternal urinary cotinine concentrations in a study of *in utero* exposure to parental smoking (Oryszczyn *et al.*, 1991). Twenty percent of the mothers smoked at least one cigarette per day during one of three trimesters. Infants whose mothers smoked or had been passively exposed to ETS had significantly higher cord blood cotinine levels than infants whose mothers neither smoked nor been exposed to ETS. However, no association was observed between cord blood IgE and maternal smoking as assessed by either questionnaire or cord blood cotinine. This study did not examine post-natal ETS exposure.

Ownby *et al.* (1991) followed 114 infants born to subscribers of a health maintenance organization in Michigan. The infants were selected from a stratified sample chosen to assure nearly equal proportions of infants from nonsmoking, light and heavy smoking households, although the definitions for each category are not stated in the report. As in the previous study, cord cotinine concentrations were measured to assess the validity of self-reported maternal smoking. Neither univariate analyses nor analyses that adjusted for the children's gender, birth weight, birth length, paternal history of allergies, maternal history of allergies or asthma, maternal visit to an allergist, history of skin testing or immunotherapy were significantly related to cord blood IgE. The authors speculated that if passive smoking induces atopy only in those with a familial tendency, such a study design might mask an association if atopics are less likely to smoke. Therefore, regression models were run both with and without adjustment for parental history of allergic disease. The association was also nonsignificant for a subgroup of infants whose parents were not atopic. When multiple regression models were used, the authors detected an association of immunoglobulin D (IgD) and paternal, but not maternal, smoking. However, the function of IgD and its relationship, if any, to the development of atopy and allergy, have not yet been elucidated.

Recently, Søyseth *et al.* (1995) investigated the relationship of prenatal and postnatal household smoking to the prevalence of atopy, defined as at least one positive skin prick test, in a cross-sectional study of 556 Norwegian school children, aged 7 to 13 years. Questionnaire assessment of ETS exposure addressed smoking by either parent during the mother's pregnancy, as well as several indices of parental postnatal smoking. In multivariate analyses that initially included age, gender, reported bronchitis before two years of age, and parental history of asthma or hay fever, Søyseth *et al.* reported that pre-natal maternal smoking was negatively associated with atopy (OR = 0.6, 95% CI = 0.4 - 0.9), while postnatal ETS exposure was not associated with this condition (OR = 1.2, 95% CI = 0.7 - 2.1). No index of paternal smoking was associated with atopy. The authors did not believe that this negative association of prenatal smoking with atopy was causal, but hypothesized rather that it may have been due to selective avoidance of smoking during pregnancy by women whose offspring might have been at higher risk of developing atopy (*e.g.*, because of a family history of allergy). Regardless of the validity of this hypothesis, these results do not indicate an increased risk of allergic sensitization due to parental smoking, either prenatally or postnatally.

Investigators have also examined both the interactive effect of passive smoke exposure in children with atopic dermatitis (AD) and subsequent development of asthma. AD is characterized by a chronic or relapsing pruritic (itchy) rash. Murray *et al.* (1990) studied 240 asthmatic children aged 6 to 17 years. They found a relationship between AD and subsequent development of asthma in children with mothers who smoked. In a reanalysis of the data (Murray *et al.*, 1992), asthmatic children with smoking mothers were found to have significantly greater asthma severity than those with non-smoking mothers. The authors concluded that passive smoking may cause asthma only in children who have a history of atopic dermatitis, while exacerbating severity in those who are already symptomatic.

In summary, whether there is a relationship between the development of atopy and pre-natal or post-natal exposure to ETS has not been as thoroughly researched as have other outcomes discussed in this report. Published investigations of this issue have produced mixed results.

6.3.2. Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease characterized by thickened mucus, a nonfunctional mucociliary clearance pathway, and recurrent and chronic pulmonary infections. Among whites in the United States, it is the most common life-threatening genetic disease, occurring in 1 in 2,500 live births. Incidence of CF is much lower in U.S. black populations, affecting only 1 in 17,000 live births. Certain patients with CF have severe pancreatic insufficiency with intestinal malabsorption and growth retardation. Life expectancy for patients with CF has improved dramatically over the past two decades. In 1978, only 18 percent of CF patients were aged 18 and older. By 1991, this had risen to 33 percent. Patients with CF are now living into the sixth and seventh decades of life (Boat and Boucher, 1994). Only a few studies have examined potential effects of ETS on patients with CF: these are summarized in Table 6.5

In a cross-sectional study, Gilljam *et al.* (1990) studied 32 Swedish children with CF, aged 1 to 20 years, 22 of whom had at least one parent who smoked one or more cigarettes per day in the home. A clinical index was computed for each child using the Shwachman score (the lower the score, the more severe the disease). The number of severe respiratory infections was assessed by the number of days of antibiotic treatment in a hospital during a one-year interval. Pulmonary function tests were administered and the number of weekly scheduled physical activities per week were counted. Gilljam *et al.* found that there was no significant association between passive smoking and clinical score; however six of seven children with low scores came from smoking families. There was a significant difference between days of antibiotic treatment in a hospital if the mother was a smoker compared to if only the father smoked ($p<0.05$). High physical activity level appeared to dampen the negative effects of ETS. Lung function was not associated with passive smoking.

In another cross-sectional study, Rubin (1990) studied 43 Canadian children (18 girls and 25 boys) aged 6 to 11 years at a CF summer camp to assess the relationship of passive smoke exposure to growth, nutritional status, lung function, clinical condition and number of hospital admissions. Over half (24) of the children came from homes with smokers and nearly 40% from families in which the mother smoked. None of the children smoked. Although statistical analyses were normalized for age, no further adjustments were made.

Hospital admission rates (defined as the total number of admissions adjusted for the child's age) were strongly correlated with number of cigarettes smoked in the home ($r = 0.58$, $p<0.0001$) for the group as a whole and for the subset of children with smoke exposure in the home. When analyses were stratified by gender, this relationship was apparent for female subjects only. A significant correlation of ETS exposure and clinical score was apparently confounded by nutritional status, attributed largely to the strong correlation between nutritional subscore and ETS exposure. In addition, those children assessed as having poor nutritional status who were exposed to passive smoke had higher admission rates than those with poor nutrition from non-smoking homes ($p=0.10$).

Rubin also found a significant interaction between lung function and ETS in relation to hospital admission rates ($p=0.05$); among children with lower lung function, smoking in the home was associated with significantly more hospitalizations. There was also a significant association between percent of predicted peak expiratory flow rate (PEFR) and smoke exposure, but no significant associations were found for other pulmonary function measures. For girls, there was a significant inverse correlation between number of cigarettes smoked per day in the home and height and weight ($p<0.05$); for boys, a near-significant correlation with height ($p=0.067$). There was no association of coughing, sputum production or nasal polyps with passive smoke exposure.

This study did not adjust for socioeconomic status (SES). However, changes in clinical status that could be related to economic barriers to health access are unlikely to have affected the results because Canada has national health insurance. Moreover, this CF population was in fairly good health, with participants scoring an average of 22 points on the 25-point Shwachman score. Although the camp population might not be representative of all children with CF, the camp was free and open to anyone with the disease. On the other hand, in epidemiological studies of ETS, SES may be a confounder, not only because people in lower SES brackets tend to have a greater prevalence of smoking, but also because their residences tend to be smaller, increasing the probability of exposure to more concentrated ETS and other household respiratory irritants that could exacerbate CF.

Campbell *et al.* (1992) studied 44 CF patients aged 1 to 22 years, who were homozygous for the F508 deletion (the most prevalent CF mutation) to examine the effect of ETS exposure on clinical status after controlling for age and SES. All patients had pancreatic insufficiency, a condition associated with more severe disease. Of the 44 patients, 22 lived in homes with light smoke exposure (1 to 2 packs per day) and 6 lived in homes with heavy exposure (3-4 packs per day). The data were analyzed using a generalized linear model. There were no significant differences between the light-exposure and no-exposure groups, so these two groups were combined in later analyses and compared to the heavy smoking group. Heavy exposure was significantly associated with disease severity as measured by the Shwachman score, FEV_1 ($p=0.007$), forced vital capacity ($p<0.0001$) and a five-fold increase in the number of pulmonary related hospital admissions ($p<10^{-6}$). Models were adjusted for age and SES. Since the heavy-exposure group contained only six people, other investigators have cautioned that the results of this study may have been due to a chance clustering of high ETS exposure and poor nutritional status. The authors did conduct a “sensitivity analysis” in which two of six people were given normal pulmonary function levels and severity scores; however this did not reduce the results to nonsignificance.

More recently, Smyth and co-workers (1994) assessed the relationship of ETS exposure as measured by questionnaire and urinary cotinine in 57 children with CF and 51 controls. The age range of both groups was 5 to 16 years. The investigators examined the relationship of ETS to pulmonary function (FEV_1 and FVC) in the CF patients. Urinary cotinine levels and ETS exposure assessed by questionnaire ("smoking index") were both significantly greater in the homes of control children. FEV_1 and FVC (both expressed as a percentage of predicted for height) were regressed on cotinine concentration, smoking index, parental occupations, and patient's age and sex. Smoking index was a significant predictor of decreased FEV_1 ($p=0.022$) and FVC ($p=0.047$): for each 10-cigarette increment in the smoking index, the investigators predicted a 4% decrement in FEV_1 and a 3% decline in FVC. However, urinary cotinine was not predictive of either measure of lung function, which Smyth *et al.* speculated might have been due to the flatness of the cotinine - lung function curve in the lowest three-fifths of the cotinine distribution. The geometric mean urinary cotinine concentration was 5.12 ng/ml, which lends credibility to the investigators' hypothesis; however, not enough detail is provided in this brief report to evaluate adequately the discrepancy between the results of the smoking index and cotinine analyses. Smyth *et al.* did not examine the relationship of ETS to either disease severity or hospitalizations in these CF patients.

Kovesi and co-workers (1993) examined relationships between household ETS exposure and several clinical parameters in 325 patients attending the Cystic Fibrosis Clinic at the Hospital for Sick Children in Toronto in 1990 to 1991. Data on household smoking were routinely obtained by clinic nurses on standardized forms, and included whether anyone in the household (including the patient) smoked cigarettes and, if so, the total number of cigarettes consumed in the home by all smokers. The age range of 1 to 42 years was considerably larger than in any of the other studies (Kovesi, personal communication), but separate analyses were done on children aged 6 to 11 for comparison to the study by Rubin (1990). The percentage of participants exposed only to maternal smoking was not identified. Given the reported mean age in both exposed and nonexposed groups, some of these patients were probably not living with their parents, which might distinguish this study population from the others described above. Comparing patients from smoking versus nonsmoking households, there were no significant differences in Shwachman scores, spirometry (FVC, FEV_1, FEF_{25-75}), height and weight percentiles, colonization by *Pseudomonas* species, and other variables. However, patients with ETS exposure were younger, with a mean age of 14.4 years versus 17.0 years for the unexposed. Linear regression analysis showed no relationship between the number of cigarettes smoked in the household and the children's weight or weight percentiles, weight for height, Shwachman or Brasfield scores (different measures of clinical status), spirometric indices, number of hospital admissions or number of days spent in the hospital. When households with smokers (n=97) were analyzed separately, similar results were obtained. When the subset of children aged 6 to 11 were analyzed, the results were similar to those obtained for the entire study population except that there was a significant inverse correlation between the number of cigarettes smoked in the household and the patients' height percentile ($r = -0.27$, $p = 0.04$).

The authors also conducted separate longitudinal analyses of spirometry, weight and height percentiles for 182 patients who had had smoking and spirometric data collected between 1977 and 1985. ANOVA was used to compare various clinical parameters among three groups: those who reported no smoke exposure in either data collection period ("NEVER"), those reporting

ETS exposure both times ("ALWAYS"), and those reporting such exposure between 1977 and 1985, but not in 1990 or 1991 ("QUIT"). A fourth "STARTED" group was too small and heterogeneous to be used in analysis. The NEVER group's height percentile increased, while this index decreased for the ALWAYS group; and even more so for the QUIT group. This same relative order was observed for changes in weight percentile and weight for height percentile. Though all groups experienced a decline in their percent predicted spirometric indices (FVC, FEV_1, FEF_{25-75}), the decrease was greatest in the QUIT group and least in the NEVER group. When the analysis was restricted to the subgroup of CF patients homozygous for the ΔF_{508} mutation, similar results were found, after an "outlying" patient with "extremely heavy smoking exposure" was excluded from the analysis.

In this large study, Kovesi *et al.* confirmed the existence of a negative dose-response relationship between household ETS exposure and linear growth in children with CF aged 6 to 11, reported previously by Rubin (1990). In the longitudinal component of the investigation, they found that exposure to household ETS was associated with growth suppression. In contrast to the findings of Campbell *et al.* (1992) and Smyth *et al.* (1994), but similar to Rubin (1990), those investigators did not find a relation between ETS exposure and lung function. In the Campbell study, which examined patients homozygous for the ΔF_{508} deletion, effects were found only in six patients with relatively high reported ETS exposure. Moreover, the distribution of reported smoking levels in the investigation by Kovesi and co-workers was such that all patients would have been classified in the "light-exposure" group in the Campbell study, thus the results of these two reports are not inconsistent.

In the Kovesi study population there was considerable inter-child variability in spirometry, which is characteristic of CF patients, making small mean lung function differences difficult to detect. Kovesi and colleagues also could not confirm the relationship between ETS and hospital admissions reported by both Rubin and Campbell *et al.* However, whereas Rubin examined age-adjusted hospitalizations over the children's lifetimes, Kovesi *et al.* appear to have examined only hospitalizations (and days in hospital) over the year preceding the children's clinic visit. Furthermore, although the initial analysis comprised a much larger study population than previous studies, the subsample of children aged 6 to 11 was not much larger than that of Rubin. In addition, the study by Kovesi *et al.* included older patients than the other five studies, although the investigators were not able to detect an interaction of age and smoking exposure on any of the outcomes. As noted above, the reported exposure distribution of ETS-exposed children in the Kovesi study was comparable to Campbell and co-workers' "light-exposure" group, for which the latter investigators found no effect of ETS exposure on hospitalizations. Thus, the results of the Kovesi study with respect to hospital admissions are not necessarily inconsistent with those reported by others. In addition, the identities of household smokers (other than the few actively smoking study participants) were not obtained: in other settings (*e.g.*, induction of childhood asthma), maternal smoking appears to be more strongly related to young children's actual ETS exposure than paternal smoking. Thus, here, as elsewhere, misclassification of exposure may have produced a bias towards the null hypothesis of no effect. Finally, in the regression analysis conducted by Kovesi et al, it appears that they did not adjust for SES, which could also have confounded the results (see above).

In part because CF is such an uncommon disease, four of these five studies have small sample sizes and low statistical power. Given this limitation, the finding that ETS is associated with hospitalizations for respiratory infection in three of four studies is striking. This relationship was observed in Rubin's (1990) study, which included relatively healthy children, and Campbell's study in which the children presumably had more severe disease. Rubin (1990) also detected interactions of ETS with the number of hospitalizations in those with lower pulmonary function and poor nutrition. While Gilljam *et al.* (1989) did not observe a direct effect of ETS on hospitalizations, they did find effects in those exposed to maternal smoking. In contrast, Kovesi *et al.* did not find any relationship between ETS exposure and hospitalizations.

The relationship between ETS exposure and pulmonary function in CF patients is less clear. Campbell *et al.* (1992) observed an association between ETS exposure and pulmonary function, whereas Gilljam *et al.* (1990), and Kovesi *et al.* (1993) in a much larger study, did not. Smyth *et al.* (1994) observed a relationship between ETS and lung function, as measured by FEV_1 and FVC, when questionnaire data were used but not when ETS was assessed using salivary cotinine levels. Rubin (1990) found an association with PEFR but not with other spirometric measures. People with CF demonstrate greater variability on pulmonary function tests than healthy subjects. This variability combined with the rarity of the disease make it difficult to demonstrate effects on pulmonary function.

Disease severity was investigated in four of the five studies. Only one study, that of Campbell *et al.* (1992) found a relationship with ETS exposure. Gilljam *et al.* (1989) found a positive but nonsignificant relationship with disease severity, Rubin's analysis was confounded by nutritional status, and Kovesi *et al.* found no effect of ETS on disease severity in their large study population. Finally, in the two studies that looked at effects on growth, both found effects in the 6- to 11- year old age group. Rubin observed age-adjusted relationships with height and weight in girls and with height in boys. Kovesi *et al.* also found a significant relationship with height by household smoking group in their longitudinal analysis.

In reviewing these five studies, it is important to note that the age ranges of the study populations were different. Two studies included children only (Smyth *et al.*, 1994; Rubin, 1990), two study populations were comprised of infants, children and young adults (Campbell, 1992; Gilljam *et al.*, 1989) and one included infants, children and young and older adults (Kovesi *et al.*, 1993). Some of the differences in study findings are potentially attributable to this variation in composition. In particular, if young children with CF are most sensitive to ETS or are likely to experience the greatest intensity of exposure, the study population of Kovesi *et al.* would have had any ETS-related effects diluted by the inclusion of relatively older participants.

In summary, although several reports suggest that passive smoke exposure can affect patients with CF, the extent and magnitude of such effects are still uncertain. The evidence for an effect on hospitalizations is compelling, while the studies are less conclusive in showing an effect on pulmonary function or disease severity. The two studies that have looked at growth have both found an inverse relationship between ETS exposure and linear growth. Because of the rarity of CF, relatively few children with CF in California are likely to be affected by ETS exposure. In all five studies, however, the proportion of CF patients with ETS exposure was quite high, ranging from 42% in the study by Kovesi *et al.* (1993) to 69% in the study by Gilljam *et al.* (1989).

TABLE 6.5: ETS EXPOSURE RELATIONSHIP WITH PULMONARY FUNCTION, HOSPITALIZATIONS AND DISEASE SEVERITY IN CHILDREN WITH CYSTIC FIBROSIS

Study	Age of Subjects (N)	ETS Exposure Prevalence	Pulmonary Function	Hospitalizations for Cystic Fibrosis	Cystic Fibrosis Severity	Growth
Gilljam *et al.* (1989)	1-20 (32)	22/32 (69%)	NS	In those exposed to maternal smoking, an effect of ETS on number of days of antibiotic treatment in hospital	Positive but not significant`	Not examined
Rubin (1990)	6-11 (43)	24/53 (56%)	Significant only for PEFR, not for FEV_1 or FVC	Significant, overall and in ETS group, but only for girl-ETS. Interaction with both poor nutrition and low pulmonary function.	Yes, but confounded by nutrition. (Unadjusted)	In girls, relationship of ETS to height and weight. In boys, only height.
Campbell (1992)	1-22 (44)	28/44 (64%)	Significant for both FEV_1 and FVC	Significant, RR=5.0 (Add CI)	Significant	Not examined.
Smyth *et al.* (1994)	5-16 (57)	33/57 (58%)	Assessment of ETS exposure by questionnaire but not cotinine related to both FEV_1 and FVC.	Not examined.	Not examined.	Not examined
Kovesi *et al.* (1993)	1-42 (325)	97/228 (43%)	NS in cross-sectional study; in longitudinal study, QUIT group was significantly worse than NEVER group	NS	NS	In 6-11 yr group, a relationship with height percentile. Relationship with height by household smoking group in longitudinal analysis

Abbreviations: N = study size; PEFR = peak expiratory flow rate; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RR = relative risk; NS = nonsignificant

6.4 Chapter Summary and Conclusions

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. ETS exposure can exacerbate asthma in children, perhaps affecting 48,000 to 120,000 children annually in California; adults may also be affected. Parental smoking is associated with an increased risk of acute lower respiratory tract illnesses in children, as well as acute and chronic otitis media with middle ear effusions. In California, ETS-related otitis media cases may result in an estimated 78,000 to 188,000 office visits per year among children under three years of age. From 18,000 to 36,000 cases of ETS-related bronchitis or pneumonia can be predicted to occur in children 18 months of age and under, based on national statistics. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS; in addition, odor annoyance from indoor exposure to ETS has been shown in several studies. Experimental studies conducted by investigators familiar with building ventilation practice suggest that, short of prohibiting indoor smoking, protection of nonsmokers against both sensory irritation and odor annoyance can only be achieved through extensive engineering measures.

There is consistent and compelling evidence that ETS is a risk factor for induction of new cases of asthma; in California, between 960 and 3,120 new cases per year may be ETS-related. In addition, chronic respiratory symptoms in children, such as cough, phlegm, or wheezing, are associated with parental smoking. While the results from all studies are not wholly consistent, there is substantial evidence that childhood exposure to ETS affects lung growth and development, as measured by small, but statistically significant decrements in pulmonary function tests; associated reductions of lung function may persist into adulthood. The effect of chronic ETS exposure upon pulmonary function in otherwise healthy adults is likely to be small, and unlikely by itself to result in clinically significant chronic disease. However, in combination with other insults (*e.g.*, prior smoking history, exposure to occupational irritants or ambient air pollutants), ETS exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms.

Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

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